The Genetic Architecture of Neurodegeneration

A Phase-Resolved Synthesis of the Genes Whose Effects Compose the Disease

Mendelian Anchors, the APOE Master Variable, and the Common-Variant Architecture Read Through the Three Temporal Phases of Alzheimer's Disease: Bioenergetic Collapse, Microglial Collapse, and Extracellular-Matrix Collapse

ONS Methodology — First Principles — Doctoral Thesis

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Collapse program, situated in the 'First Principles' layer of AdultCognitiveDisease.com and companion to the Collapse trilogy and the Tryptophan Partition volume.

“The genes are not a list. They are an architecture, and the architecture is temporal. A person’s inherited risk is most informatively read not as a single number but as a profile that says when, in the life course, that risk becomes load-bearing.”

— ONS Methodology First Principles, 2026

For Oskar Fischer, whose first description of the senile plaque in 1907 predates the molecular genetics that would identify its biochemical substrate by eighty-four years — and for the patients and families of the Colombian E280A kindred, whose participation in three decades of longitudinal observation has supplied the human evidence on which much of this dissertation rests.

ONS METHODOLOGY — FIRST PRINCIPLES

Companion to the Collapse Trilogy

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition

V. The Genetic Architecture of Neurodegeneration □ this volume

The Collapse trilogy and its companion volumes have characterized the three sequential temporal phases of Alzheimer's disease — the bioenergetic phase in the locus coeruleus and noradrenergic projection system, the microglial phase in the hippocampus and oligodendrocyte populations, and the extracellular-matrix phase in perineuronal nets ensheathing parvalbumin interneurons. The present volume, sitting in the 'First Principles' layer of the AdultCognitiveDisease.com program, reads the inherited-risk architecture — Mendelian, polygenic, and effector — through this same three-phase lens.

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Abstract

The genetic architecture of late-onset neurodegenerative disease is one of the best-characterized in human biology and yet remains the most theoretically under-integrated. Genome-wide association studies in Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis have together identified more than 150 genome-wide significant loci, and rare-variant sequencing has identified an additional set of high-penetrance Mendelian genes that delineate canonical disease subtypes. The conventional reading of this evidence is gene-by-gene: each locus is interpreted as a discrete risk factor, assigned an odds ratio, mapped to a putative effector pathway, and entered into a polygenic risk score whose linearity is rarely examined. This dissertation advances a different reading. It argues that the genes implicated in neurodegeneration are not a flat list of risk modifiers but a temporally structured architecture, in which different genes are load-bearing at different biological moments — specifically, the three sequential temporal phases articulated by the Collapse trilogy: a bioenergetic phase localized to the noradrenergic projection system (age 20–50), a microglial-homeostatic phase localized to the hippocampus and oligodendrocyte populations (age 50–70), and an extracellular-matrix phase localized to perineuronal nets ensheathing parvalbumin-positive interneurons (age 70 and beyond).

The dissertation is organized in nine analytical chapters. Chapter I treats the Mendelian architecture across AD, FTD, PD, ALS, and HD, identifying convergent themes — proteostasis failure, mitochondrial quality-control failure, RNA-binding-protein dysregulation, axonal vulnerability — that span syndromic boundaries and that anticipate, at the highly penetrant end of the allelic spectrum, the same effector pathways that the common-variant architecture implicates at small effect sizes. Chapter II treats APOE as the single master variable of late-onset Alzheimer's risk, the only gene whose effect size approaches an order of magnitude at population frequencies above 5%, and the only gene that touches all three temporal phases through distinct mechanisms — lipid handling in Phase I, microglial state in Phase II, and synaptic-PNN modulation in Phase III. Chapter III examines the genes

load-bearing in Phase I — the NAD□ metabolic network (NMNAT2, SARM1, NAMPT, CD38, NMRK1, NMRK2, the sirtuin family), the mitochondrial quality-control machinery (PINK1, PRKN, OPA1, MFN1, MFN2, DRP1, POLG, TFAM), the autophagy-lysosomal apparatus (TFEB, TFE3, ATG7, BECN1, MAP1LC3B, OPTN, NDP52, SQSTM1), the integrated stress response (ATF4, CHOP/DDIT3, GADD34, PERK, GCN2, PKR, HRI), and the locus-coeruleus identity program (TH, DBH, SLC18A2, ADRA2A). Chapter IV examines the genes load-bearing in Phase II — TREM2 and its TYROBP/DAP12 adapter, the CD33 and MS4A clusters, PLCG2 and ABI3 and INPP5D, the complement axis (C1QA/B/C, C3, C4A, C4B, CR1, ITGAM), the homeostatic-microglial identity program (TGFB1, SMAD3, SALL1, MEF2C, SPI1/PU.1, P2RY12, CX3CR1), the ferroptosis defense machinery (GPX4, FSP1/AIFM2, NFE2L2, SLC7A11, GCLC), the ferroptosis execution program (ACSL4, LPCAT3, ALOX15, ALOX5), the oligodendroglial identity program (MBP, MOG, PLP1, MAG, OLIG2), and the lipid-handling axis (ABCA7, ABCA1, CLU, PLD3, TREM2-ApoE coupling). Chapter V examines the genes load-bearing in Phase III — the perineuronal-net structural program (ACAN, BCAN, NCAN, VCAN, TNR, HAPLN1, HAPLN4), the proteoglycan-synthesis program (CSGALNACT1/2, CHST3, CHST11, HAS1-3, B3GAT1), the matrix-degradation program (MMP9, MMP2, MMP3, ADAMTS4, ADAMTS5), the matrix-inhibitor program (TIMP1, TIMP2, TIMP3, RECK), the parvalbumin-interneuron identity program (PVALB, GAD1, GAD2, KCNC1, KCNC2, KCNC3, LHX6, NKX2-1, ERBB4, NRG1, GPHN), and the endocytic-trafficking GWAS axis (BIN1, PICALM, SORL1, CD2AP, EPHA1). Chapter VI develops the gene–gene interaction landscape, with particular attention to APOE × TREM2, APOE × ABCA7, TREM2 × PLCG2, and the broader question of whether polygenic risk scores constructed under linear additive assumptions systematically underestimate combinatorial risk at the tail. Chapter VII analyzes the relative importance of these genes through three complementary metrics — odds ratio at population frequency, variance explained in polygenic risk scores, and effector-pathway centrality in functional network analyses — and shows that the three metrics rank the genes differently, with implications for both biology and trial design. Chapter VIII develops the therapeutic landscape, mapping each phase to genotype-guided interventions: PARP inhibitors and NAD□ precursors for Phase I, TREM2 agonists and ferroptosis inhibitors for Phase II, MMP-9 inhibitors and PNN-protective agents for Phase III. Chapter IX concludes.

The dissertation argues that the genetic architecture of neurodegeneration is not flat. It is layered. The Mendelian genes anchor the system at high penetrance; APOE bridges the layers at population frequency; and the common-variant architecture distributes risk across the three temporal phases such that any given individual's polygenic risk profile is most informatively read as a *phase-weighted* profile — a profile that says not how much risk a person carries but in which biological moment that risk is most likely to manifest.

Keywords: neurodegeneration genetics, Alzheimer's disease, APOE, TREM2, MAPT, SNCA, APP, PSEN1, NAD□ metabolism, mitochondrial quality control, ferroptosis, perineuronal nets, parvalbumin interneurons, MMP-9, polygenic risk, temporal pharmacology, ONS Methodology, Collapse trilogy

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1. Introduction

1.1 The Research Problem

The genetic architecture of late-onset neurodegenerative disease is conventionally presented as a list. The list is long — for Alzheimer's disease alone, Bellenguez et al. (2022) reported 75 genome-wide significant loci in a meta-analysis of more than 1.1 million individuals, expanding the earlier landmark counts of 21 loci (Lambert et al., 2013), 25 loci (Kunkle et al., 2019), and 38 loci (Wightman et al., 2021). For Parkinson's disease, the most recent GWAS reports 90+ loci (Nalls et al., 2019; Kim et al., 2024); for frontotemporal dementia, the landscape is dominated by *MAPT*, *GRN*, and *C9ORF72* but augmented by common-variant loci at *TMEM106B*, *HLA-DRA*, and others; for amyotrophic lateral sclerosis, more than 40 loci have been identified, with *C9ORF72* repeat expansions accounting for the largest single contribution (van Rheenen et al., 2021). Each locus is annotated with an effect-size estimate, a putative effector gene assignment derived from expression quantitative trait loci, single-cell expression atlases, or perturbation screens, and increasingly, a credible-set posterior inclusion probability. The list is then aggregated into a polygenic risk score, which performs reasonably well at separating cases from controls in research cohorts (Escott-Price et al., 2015; Leonenko et al., 2021) and reasonably poorly at clinical-grade individual prediction.

What the list does not do is tell us *when* in the life course each gene matters. The list is flat. The polygenic risk score is a single number. The implicit model is one in which all the genes act simultaneously, throughout life, in a single tissue compartment, with effects that aggregate linearly into a unitary disease state. This model is convenient. It is also wrong in three distinct and well-characterized ways. First, the diseases themselves are not single states — Alzheimer's disease in particular is increasingly understood as a sequential pathology that runs from a noradrenergic and serotonergic brainstem phase (initiated by NAD□ depletion and PARP-1 hyperactivation in projection neurons), through a hippocampal microglial phase (driven by oligodendrocyte ferroptosis, microglial-state collapse, and the entry of disease-associated microglia), to a cortical extracellular-matrix phase (driven by MMP-9 hyperactivity, perineuronal-net degradation, and the loss of parvalbumin-interneuron gamma-frequency drive). The temporal-pharmacology

framework that has emerged from the Collapse trilogy — *Convergent Synaptic Collapse*, *Homeostatic Microglial Collapse*, *Bioenergetic Collapse* — asserts that these three phases are biochemically distinct, anatomically distinct, and therapeutically distinct, and that the genes that load-bear each phase are not the same set. Second, the genes themselves act in distinct cell types, and the cell types occupy distinct positions in the disease trajectory; a gene that is expressed primarily in microglia cannot be load-bearing in a phase in which microglia have not yet been recruited, and a gene that is expressed primarily in oligodendrocytes cannot be load-bearing in a phase in which the oligodendrocyte compartment is still intact. Third, the effect sizes of the common-variant genes are small in absolute terms but become large when conditioned on the right biological moment — the polygenic effect at population frequency conceals a substantial within-phase effect that is invisible to the flat model.

This dissertation addresses the question: **What is the genetic architecture of neurodegeneration when read through the three temporal phases of the disease trajectory?** The thesis advanced is that the genetic architecture is phase-resolved, that different sets of genes are load-bearing in different phases, and that the failure to model this phase structure is the principal explanation for both the disappointing performance of single-target therapeutics in late-stage trials and the disappointing clinical utility of flat polygenic risk scores.

1.2 Significance

The significance of the phase-resolved reading is fourfold. First, it supplies a biological interpretation of the long-observed heterogeneity of late-onset Alzheimer's disease — the observation that some patients present with predominantly amnestic syndromes, others with posterior cortical atrophy, others with logopenic aphasia, others with frontal-executive variants. The conventional reading attributes this heterogeneity to anatomical variation in pathology accumulation; the phase-resolved reading attributes it to differential weighting of the three phases in the underlying disease trajectory, with each patient's phenotype reflecting which phase was most aggressive in their particular biological history. The phase-weighted polygenic risk score predicts this directly: a person with a Phase III–weighted PRS should preferentially develop a synaptic-loss-dominant clinical picture, while a person with a Phase II–weighted PRS should preferentially develop a glial-inflammation-dominant clinical picture.

Second, the phase-resolved reading reorganizes the therapeutic landscape. Where each gene in a flat PRS suggests a candidate drug target, the phase-resolved reading instead suggests a candidate drug *and a candidate biological moment*. A PARP-1 inhibitor that preserves NAD□ in the locus coeruleus during Phase I serves an entirely different purpose than a ferroptosis inhibitor that protects oligodendrocytes during Phase II or an MMP-9 inhibitor that preserves perineuronal nets during Phase III. The phase-resolved reading therefore makes a clear prediction about clinical trial design: trials enriched for phase-appropriate participants — by age, by biomarker, and ideally by phase-weighted PRS — should show effect sizes substantially larger than trials that draw indiscriminately from the late-life population.

Third, the phase-resolved reading clarifies the meaning of effect size. The conventional metric — the per-allele odds ratio at the population frequency of the risk allele — averages across phases and therefore systematically understates the within-phase effect. *TREM2* R47H carries a population-averaged odds ratio of approximately 3.0 for Alzheimer's disease (Guerreiro et al., 2013; Sims et al., 2017); the within-Phase-II effect is plausibly much larger, since outside Phase II the gene is not load-bearing. The conventional metric thus penalizes phase-specific genes and rewards phase-spanning genes — a bias that has driven the field toward APOE-like targets and away from cell-type-specific ones.

Fourth, the phase-resolved reading supplies the integrative framework in which the Mendelian and common-variant architectures cohere. The Mendelian genes (APP, PSEN1, PSEN2 for AD; MAPT, GRN, C9ORF72 for FTD; SNCA, LRRK2, GBA for PD; HTT for HD; SOD1, TARDBP, FUS for ALS) are individually rare but together describe the highly penetrant end of the spectrum, and their effector pathways anticipate the common-variant architecture. APP/PSEN biology converges on amyloid-precursor processing and γ-secretase activity, which the common variants modulate through endocytic-trafficking genes (BIN1, PICALM, SORL1, CD2AP). MAPT biology converges on tau homeostasis, which the common variants modulate through MAPT-haplotype-tagging SNPs and through proteostasis modifiers. SNCA biology converges on α-synuclein aggregation, which the common variants modulate through GBA and the lysosomal pathway. C9ORF72 biology converges on RNA-binding-protein dysregulation, which the common variants modulate through TARDBP, FUS, and TMEM106B. The dissertation argues that all four of these convergence axes — amyloid-endocytic, tau-proteostatic, synuclein-lysosomal,

RNA-binding-stress — are *Phase II convergences* in the sense that they require the recruitment of microglia and the failure of homeostatic proteostasis, and that the Mendelian genes therefore enter the phase structure principally by accelerating the entry into Phase II rather than by occupying a distinct phase of their own.

1.3 Scope and Limitations

This dissertation is a synthetic review and integrative argument, not a report of original experimental or bioinformatic data. Its contribution is the integration of three distinct genomic literatures — the Mendelian-genetics literature on the high-penetrance early-onset forms of neurodegeneration, the GWAS literature on the common-variant architecture of late-onset disease, and the single-cell-transcriptomics literature on the cell-type expression of risk genes — into a single analytical schema centered on the three temporal phases of Alzheimer's disease. The work draws principally on AD because the temporal-phase framework was developed for AD, but it engages comparably with PD, FTD, ALS, and HD where the Mendelian and pathway evidence supports cross-disease integration.

The dissertation does not attempt to resolve the longstanding question of whether neurodegeneration is a single disease with multiple phenotypic expressions or multiple distinct diseases with overlapping presentations. The phase-resolved framework is consistent with either reading. What it does assert is that even if the diseases are nominally distinct, the *phases through which they progress* are biochemically convergent — every neurodegeneration we know runs through a bioenergetic phase, a microglial-inflammatory phase, and a synaptic-matrix phase, and the genes that load-bear each phase are largely the same across the diseases. The phase architecture is therefore deeper than the disease taxonomy, and the genetic architecture is most informatively read at the phase level.

The dissertation also does not attempt to resolve the question of whether the three phases are strictly sequential or partially overlapping. The evidence supports a predominantly sequential reading — the locus coeruleus shows pathology in the third and fourth decades, well before microglial activation in the medial temporal lobe in the sixth decade, well before perineuronal-net loss in the cortex in the eighth decade — but with substantial overlap, particularly between Phases II and III, where ferroptosis-driven oligodendrocyte loss and MMP-9-driven matrix degradation can co-occur for two decades or more. The framework treats phase boundaries as soft and

probabilistic.

2. Literature Review and Methodology

2.1 The Mendelian Era (1991–2011)

The molecular genetics of neurodegeneration began with the identification of the *APP* gene as the source of the amyloid precursor whose cleavage products accumulate in the senile plaques of Alzheimer's disease (Kang et al., 1987; Goate et al., 1991). Mutations in *APP*, principally in or near the β- and γ-secretase cleavage sites, were identified in pedigrees with autosomal dominant early-onset AD and were shown to alter the ratio of Aβ40 to Aβ42 or to enhance overall Aβ production (Citron et al., 1992; Suzuki et al., 1994). The subsequent identification of *PSEN1* on chromosome 14 (Sherrington et al., 1995) and *PSEN2* on chromosome 1 (Levy-Lahad et al., 1995; Rogaev et al., 1995) as the catalytic components of γ-secretase, with more than 200 pathogenic missense mutations identified across the two genes, established the amyloid hypothesis as the dominant molecular framework for autosomal dominant AD. The frontotemporal dementia field was anchored by the identification of *MAPT* mutations in tauopathy pedigrees (Hutton et al., 1998; Spillantini et al., 1998), followed by *GRN* (progranulin) mutations in TDP-43-proteinopathy pedigrees (Baker et al., 2006; Cruts et al., 2006), and culminating in the identification of the *C9ORF72* hexanucleotide repeat expansion as the most common cause of both familial FTD and familial ALS (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The Parkinson's disease field was anchored by *SNCA* (Polymeropoulos et al., 1997), *LRRK2* (Paisán-Ruíz et al., 2004; Zimprich et al., 2004), *PRKN* (Kitada et al., 1998), *PINK1* (Valente et al., 2004), *DJ-1/PARK7* (Bonifati et al., 2003), *VPS35* (Vilariño-Güell et al., 2011; Zimprich et al., 2011), and *GBA* (Sidransky et al., 2009). Huntington's disease was the first to be solved (Huntington's Disease Collaborative Research Group, 1993). The ALS field was anchored by *SOD1* (Rosen et al., 1993), *TARDBP* (Sreedharan et al., 2008), *FUS* (Kwiatkowski et al., 2009), and *C9ORF72*.

The Mendelian era established a small number of canonical lessons. First, several distinct gene families converge on a small number of effector pathways: APP and PSEN1/2 converge on Aβ; MAPT and GRN converge on neuronal proteostasis (via tau and progranulin-regulated lysosomal function); SNCA, GBA, LRRK2, and VPS35

converge on α-synuclein aggregation and lysosomal-autophagic clearance; PRKN, PINK1, and DJ-1 converge on mitochondrial quality control; TARDBP, FUS, and C9ORF72 converge on RNA-binding-protein dysregulation and stress-granule biology. Second, the Mendelian genes are individually rare but disproportionately informative: each one identifies an effector pathway through which the much larger common-variant architecture can be interpreted. Third, the phenotypic boundaries between syndromes are not respected by the genes — *C9ORF72* expansions cause both FTD and ALS; *MAPT* mutations cause FTD, PSP, and CBD; *GBA* mutations cause both PD and Lewy body dementia; *TARDBP* mutations cause both ALS and FTD — and the pathway-level convergence is therefore deeper than the syndrome-level taxonomy.

2.2 The GWAS Era (2009–2026)

The genome-wide association study (GWAS) era began for AD with the identification of *CR1*, *CLU*, and *PICALM* as common-variant susceptibility loci (Harold et al., 2009; Lambert et al., 2009; Hollingworth et al., 2011; Naj et al., 2011), followed by the identification of *BIN1*, *MS4A6A*/*MS4A4E*, *CD33*, *EPHA1*, *CD2AP*, and *ABCA7*. The subsequent meta-analyses (Lambert et al., 2013; Kunkle et al., 2019; Wightman et al., 2021; Bellenguez et al., 2022) expanded the count past 75 loci, with several large independent loci added in each successive meta-analysis. The PD GWAS literature followed a parallel arc, with the most recent meta-analysis (Nalls et al., 2019, and subsequent updates) identifying 90+ loci, including loci near *SNCA*, *LRRK2*, *GBA*, *MAPT*, and many novel genes such as *TMEM175*, *RAB7L1*, *VPS13C*, and *DGKQ*. The ALS GWAS literature, while smaller in sample size, has identified more than 40 loci centered on RNA-binding-protein biology, cytoskeletal dynamics, and the integrated stress response.

The GWAS era established its own set of canonical lessons. First, the per-allele effects of common variants are small — typically odds ratios between 1.05 and 1.20 — but together account for a substantial fraction of disease heritability (Witoelar et al., 2017; Escott-Price et al., 2017). Second, the genes implicated by common variants overlap only modestly with the genes implicated by Mendelian inheritance — APOE is in both lists, MAPT is in both lists, GBA is in both lists, but the bulk of the GWAS catalog identifies novel genes that were not previously implicated by Mendelian analysis. Third, the cell-type expression of the GWAS-identified genes is heavily biased toward microglia: single-cell expression analyses of AD GWAS loci

consistently show that the implicated genes are expressed at higher levels in microglia than in any other cell type (Gjoneska et al., 2015; Karch and Goate, 2015; Novikova et al., 2021), and that the microglial expression is preferentially activated in disease-associated microglial subpopulations (Keren-Shaul et al., 2017; Olah et al., 2020). The microglial enrichment is so strong that the AD GWAS architecture is sometimes described as primarily a microglial disorder (Efthymiou and Goate, 2017; Sierksma et al., 2020), with the convergent interpretation that the genes are most informative when read in their phase-II context.

2.3 The Single-Cell and Phase-Resolved Eras (2017–2026)

The advent of single-cell transcriptomics in postmortem AD brain (Mathys et al., 2019; Grubman et al., 2019; Lau et al., 2020; Zhou et al., 2020; Olah et al., 2020; Mathys et al., 2023; Green et al., 2024) provided the first cell-type-resolved expression atlas of AD risk genes and confirmed that the microglial enrichment of the GWAS catalog is genuine and not an artifact of expression-level differences. The single-cell data also identified novel cell-state transitions — disease-associated microglia (DAM), lipid-droplet-accumulating microglia (LDAM), MGnD microglia, the loss of homeostatic markers (P2RY12, P2RY13, CX3CR1, TMEM119), and the gain of activation markers (ITGAX, CLEC7A, SPP1, CST7, AXL) — that supplied a finer-grained phenotypic vocabulary for microglial-phase biology than the bulk-tissue literature had supported. The oligodendrocyte literature added a parallel set of state transitions, with the identification of disease-associated oligodendrocyte (DOL) subpopulations marked by ferroptosis-vulnerability signatures (Pandey et al., 2022; Kenigsbuch et al., 2022). The astrocyte literature identified A1/A2 polarization (Liddelow et al., 2017) and the broader spectrum of reactive astrocyte states. The neuronal literature identified vulnerable subpopulations in entorhinal cortex (Leng et al., 2021), locus coeruleus (Kelberman et al., 2024), and elsewhere.

The phase-resolved reading of this evidence — which is the framework of the present dissertation — synthesizes the single-cell, GWAS, and Mendelian literatures by mapping each gene to the cellular compartment in which it is expressed, mapping that compartment to the temporal phase in which it is load-bearing, and re-reading the genetic architecture as a three-layer structure with distinct phase-specific gene sets and a small number of phase-spanning master variables (principally APOE and, to a lesser extent, TREM2). The synthesis is consistent with the temporal-pharmacology framework articulated in the Collapse trilogy and with the

broader literature on age-stratified disease trajectories.

2.4 Methodology of the Present Dissertation

The dissertation employs an integrative methodology that combines four sources of evidence. First, the Mendelian-genetics catalog from OMIM, ClinVar, and disease-specific consortia is used to identify the high-penetrance core. Second, the GWAS meta-analyses cited in §2.2 are used to identify the common-variant architecture. Third, the single-cell expression atlases cited in §2.3 are used to assign each gene to its principal cell type of expression. Fourth, the temporal-phase framework articulated in the Collapse trilogy is used to assign each cell type to its phase of load-bearing. Genes are then organized into chapters by phase, with phase-spanning genes treated in Chapter II (APOE) and Chapter VI (gene–gene interactions).

The dissertation does not attempt to be a systematic review in the formal sense — it is an integrative synthesis, not a meta-analysis — but it is exhaustive within scope: every gene that has been replicated at genome-wide significance in any of the four canonical neurodegenerative diseases is touched on at some level, with the more important genes treated at length and the less important genes touched on in context.

3. Chapter I — The Mendelian Architecture: Convergent Themes Across Syndromic Boundaries

3.1 The Amyloid Cluster: APP, PSEN1, PSEN2

The amyloid cluster is the historical core of Alzheimer's disease genetics. *APP* (chromosome 21q21.3) encodes the 695- to 770-residue transmembrane amyloid precursor protein, whose sequential cleavage by β-secretase (BACE1) and γ-secretase generates the Aβ peptides that accumulate in senile plaques. The *APP* mutations that cause autosomal dominant AD cluster at three sites: the β-secretase cleavage site (the Swedish K670N/M671L mutation, which enhances BACE1 cleavage and total Aβ production), the γ-secretase cleavage site (the London V717I mutation and related variants, which shift the Aβ40:Aβ42 ratio toward the more aggregation-prone Aβ42), and the central α-secretase cleavage site within the Aβ peptide itself (the Arctic E693G mutation, which destabilizes Aβ and enhances oligomer formation). The Icelandic A673T variant is the only known protective *APP* variant in humans and reduces lifetime AD risk by approximately 50% by impairing β-secretase cleavage (Jonsson et al., 2012). The protective A673T variant supplies the strongest single piece of human genetic evidence for the amyloid hypothesis — it is the inverse of every other *APP* mutation, and it acts at the same biochemical step, but in the protective direction.

PSEN1 (chromosome 14q24.2) and *PSEN2* (chromosome 1q42.13) encode the two alternative catalytic subunits of γ-secretase, the multi-subunit aspartyl-protease complex that performs the intramembrane cleavage of APP to generate the Aβ C-terminus. PSEN1 is the more common Mendelian cause of EOAD, with more than 200 pathogenic missense mutations identified, the great majority of which alter γ-secretase processivity in a way that shifts the Aβ40:Aβ42 ratio toward Aβ42. PSEN2 mutations are less common and typically produce somewhat later onset. The PSEN1 E280A "paisa" mutation, segregating in a large Colombian kindred, has supplied the field's most rigorous prospective study of the AD trajectory (Quiroz et al., 2018; Lopera et al., 2023) and has identified protective modifiers — most notably the *APOE3* Christchurch variant (R136S; Arboleda-Velasquez et al., 2019), homozygous in its single reported carrier, and a heterozygous *RELN-COLBOS* variant (Lopera et al., 2023) — each of which delayed onset by 20+ years.

The amyloid cluster locates its load-bearing biology in Phase I and Phase II. The Aβ peptide is generated chronically across the life course, and the imbalance between production and clearance that the mutations introduce manifests first as a slow accumulation in cerebral parenchyma decades before symptom onset, with eventual recruitment of microglia and astrocytes that defines the entry into Phase II. PSEN1 in particular has direct mitochondrial and ER-stress consequences (Area-Gomez et al., 2009, 2012, 2018) that situate its Phase I contribution in the mitochondria-associated-membrane (MAM) compartment.

3.2 The Tauopathy Cluster: MAPT, GRN, C9ORF72, TMEM106B

MAPT (chromosome 17q21.31) encodes the microtubule-associated protein tau, the principal cytoskeletal protein of axons and the substrate of the neurofibrillary tangles of AD. *MAPT* mutations cause autosomal dominant FTD with parkinsonism (FTDP-17T), progressive supranuclear palsy, and corticobasal degeneration; intronic mutations alter the splicing of exon 10 and shift the 3R:4R tau isoform ratio, while exonic mutations alter microtubule binding or aggregation propensity. The *MAPT* H1 vs H2 haplotypes, defined by a 900-kb inversion, are strongly associated with PSP (H1 confers risk) and modestly associated with AD; the H1c sub-haplotype enhances tau expression and represents one of the few common-variant signals to act directly on the disease-defining protein.

GRN (chromosome 17q21.31) encodes progranulin, a secreted glycoprotein with autocrine and paracrine effects on microglial activation, lysosomal function, and neuronal survival. Heterozygous loss-of-function *GRN* mutations produce TDP-43-positive FTD by haploinsufficiency; homozygous loss produces neuronal ceroid lipofuscinosis. Progranulin's principal cellular function is in the lysosome, where it is processed to granulins and modulates lysosomal proteases including cathepsin D and cathepsin L (Tanaka et al., 2017; Holler et al., 2017); progranulin loss therefore couples FTD pathogenesis directly to the lysosomal-autophagic axis that organizes Phase I bioenergetics.

C9ORF72 (chromosome 9p21.2) carries a hexanucleotide GGGGCC repeat in its first intron whose pathological expansion (>30 repeats, typically hundreds to thousands) is the most common Mendelian cause of both FTD and ALS in Europeans. The expansion produces three mechanisms of pathology — haploinsufficiency of the C9ORF72 protein (which functions as a DENN-domain GEF

for Rab8/Rab39 and regulates autophagy), RNA foci that sequester RNA-binding proteins, and dipeptide-repeat proteins translated through repeat-associated non-ATG (RAN) translation — and produces TDP-43-positive cytoplasmic inclusions that are the histopathological hallmark of C9-ALS/FTD.

TMEM106B is the strongest common-variant modifier of *GRN*-associated FTD (Van Deerlin et al., 2010) and is independently associated with TDP-43 pathology in primary age-related tauopathy and limbic-predominant TDP-43 encephalopathy (LATE). TMEM106B is a lysosomal membrane protein whose C-terminus is processed to amyloid-like fibrils in aged human brain (Schweighauser et al., 2022; Chang et al., 2022); the fibrils may themselves be a disease-relevant species or a marker of lysosomal stress.

The tauopathy cluster locates its load-bearing biology in Phases I and II. Tau homeostasis depends on autophagy, mitochondrial function, and the integrated stress response (Phase I); the conversion of soluble hyperphosphorylated tau to the insoluble tangle phase depends on microglial activation and TDP-43 stress-granule biology (Phase II).

3.3 The Synucleinopathy Cluster: SNCA, LRRK2, GBA, PRKN, PINK1, DJ-1, VPS35

SNCA (chromosome 4q22.1) encodes α-synuclein, the principal protein of Lewy bodies. Three missense mutations (A53T, A30P, E46K) and *SNCA* multiplications (duplications and triplications) cause autosomal dominant PD; the multiplications are particularly informative because they demonstrate a clean dose–response between α-synuclein level and disease severity. Common-variant signals near *SNCA* — including SNPs in the 3′ UTR and the REP1 promoter dinucleotide repeat — modulate α-synuclein expression and represent the strongest GWAS signal in PD.

LRRK2 (chromosome 12q12) encodes leucine-rich repeat kinase 2, a large multi-domain protein with GTPase and serine/threonine kinase activity. The G2019S mutation in the kinase domain is the most common Mendelian cause of PD in Europeans (carrier frequency ~1% in Ashkenazi Jewish and North African Berber populations) and produces dopaminergic neuronal loss indistinguishable from idiopathic PD. LRRK2 phosphorylates a subset of Rab GTPases (Steger et al., 2016) and regulates lysosomal, ciliary, and endolysosomal trafficking; the G2019S mutation enhances kinase activity, and selective LRRK2 kinase inhibitors are in active clinical

development.

GBA (chromosome 1q22) encodes the lysosomal glucocerebrosidase that catabolizes glucosylceramide. Homozygous loss-of-function *GBA* mutations cause Gaucher disease; heterozygous mutations are the single largest genetic risk factor for sporadic PD (Sidransky et al., 2009; Schapira, 2015), with carrier frequencies of 5–10% in non-Ashkenazi PD cohorts and 15–20% in Ashkenazi PD cohorts. GBA-driven PD has earlier onset, faster progression, and a higher incidence of dementia and cognitive impairment than idiopathic PD. The mechanism couples lysosomal glucosylceramide accumulation to α-synuclein aggregation through reduced lysosomal proteolytic capacity.

PRKN (chromosome 6q26), *PINK1* (chromosome 1p36.12), and *DJ-1/PARK7* (chromosome 1p36.23) cause autosomal recessive early-onset PD and converge on the mitophagy axis: PINK1 is a mitochondrial-membrane-targeted kinase that, on mitochondrial depolarization, accumulates on the outer mitochondrial membrane and phosphorylates ubiquitin and Parkin (Narendra et al., 2008, 2010); Parkin is an E3 ubiquitin ligase that, once activated, ubiquitinates outer-membrane proteins and recruits the autophagy machinery to degrade depolarized mitochondria. DJ-1 is a redox-sensing protein whose loss compromises mitochondrial complex I function and antioxidant defense. The PINK1–Parkin axis is the load-bearing axis of mitochondrial quality control and locates PD genetics squarely in Phase I.

VPS35 (chromosome 16q11.2) encodes a core component of the retromer complex, which sorts cargo from the endosome back to the trans-Golgi network. The D620N mutation causes late-onset autosomal dominant PD by impairing retromer function (Vilariño-Güell et al., 2011; Zimprich et al., 2011), and retromer dysfunction has been implicated in both PD and AD (Small and Petsko, 2015), connecting the synucleinopathy and amyloid clusters through a shared endolysosomal substrate.

3.4 The ALS/FTD Cluster: SOD1, TARDBP, FUS, C9ORF72, CHCHD10, TBK1

SOD1 (chromosome 21q22.11) encodes copper-zinc superoxide dismutase, the first Mendelian ALS gene identified (Rosen et al., 1993). More than 150 *SOD1* mutations cause autosomal dominant ALS, principally through a gain-of-function misfolding mechanism that produces cytoplasmic aggregates, mitochondrial dysfunction, and a non-cell-autonomous toxicity that recruits microglial activation. The successful clinical development of tofersen (an antisense oligonucleotide that lowers *SOD1* expression) and its approval for *SOD1*-ALS in 2023 supplies the first disease-modifying genetic therapy in a Mendelian neurodegeneration and validates the principle that lowering the toxic gene product can rescue disease trajectory even after symptom onset (Miller et al., 2022).

TARDBP (chromosome 1p36.22) and *FUS* (chromosome 16p11.2) encode RNA-binding proteins (TDP-43 and FUS, respectively) whose mutations cause ALS and FTD. Both proteins are normally predominantly nuclear, both contain low-complexity domains that drive phase separation into nuclear bodies and stress granules, and both produce cytoplasmic mislocalization and aggregation in disease. The unifying biology is the failure of the stress-granule dissolution program — the integrated stress response normally allows stress granules to assemble and disassemble reversibly, but in disease the granules persist, mature, and ultimately convert to amyloid-like aggregates that sequester the RNA-binding proteins out of the nucleus and produce cytoplasmic gain-of-toxicity (Mackenzie et al., 2017; Bowden and Dormann, 2020).

CHCHD10 and *CHCHD2* encode coiled-coil-helix-coiled-coil-helix domain proteins of the mitochondrial intermembrane space; mutations cause a spectrum of ALS, FTD, and PD with prominent mitochondrial dysfunction. *TBK1* mutations cause ALS-FTD through impaired autophagy and STING signaling. The ALS/FTD genetic architecture therefore re-anchors the convergent theme of Phase I biology — mitochondrial quality control, autophagy, and the integrated stress response — at the highly penetrant end of the allelic spectrum.

3.5 The Polyglutamine Diseases: HTT, ATXN1/2/3/7, AR

HTT (chromosome 4p16.3) encodes huntingtin, a large scaffold protein with widespread roles in vesicular trafficking, autophagy, and transcriptional regulation. The pathogenic CAG-repeat expansion in exon 1 (>36 repeats, typical disease onset 35–45 years with 40+ repeats) produces a polyglutamine tract that drives huntingtin aggregation, transcriptional dysregulation, mitochondrial dysfunction, and selective vulnerability of medium spiny neurons of the striatum. The ATXN1, ATXN2, ATXN3, and ATXN7 polyglutamine expansions produce the corresponding spinocerebellar ataxias. *ATXN2* intermediate-length expansions (27–33 repeats) are a risk factor for ALS (Elden et al., 2010), supplying a direct genetic bridge between the polyglutamine and the RNA-binding-protein literatures.

3.6 Synthesis: Five Convergent Themes

The Mendelian architecture across AD, FTD, PD, ALS, and HD converges on five effector themes that the dissertation will return to throughout. (1) **Proteostasis** — protein folding, the integrated stress response, autophagy-lysosomal degradation, and the ubiquitin-proteasome system — is implicated by APP/PSEN, MAPT/GRN, SNCA/GBA/LRRK2, and TARDBP/FUS. (2) **Mitochondrial quality control** — the PINK1–Parkin mitophagy axis, complex I integrity, MAM signaling — is implicated by PRKN/PINK1/DJ-1, CHCHD10, and indirectly by PSEN1 (through MAM). (3) **Endolysosomal trafficking** — retromer, Rab GTPases, lysosomal acidification — is implicated by VPS35, LRRK2, GBA, GRN, and TMEM106B. (4) **RNA-binding-protein and stress-granule biology** — phase separation, granule dissolution, nuclear-cytoplasmic transport — is implicated by TARDBP, FUS, C9ORF72, and ATXN2. (5) **Cytoskeletal-axonal integrity** — microtubule binding, axonal transport, and the axonal NAD□ axis — is implicated by MAPT and indirectly by SOD1, HTT, and SNCA through axonal-trafficking defects.

The five themes do not partition into the three phases at equal weight. Themes (1), (2), and (5) are predominantly Phase I biology — they describe the substrate-level vulnerability that the projection-neuron compartment exhibits decades before symptom onset. Theme (3) spans Phases I and II — endolysosomal failure begins in projection neurons and accelerates with microglial recruitment. Theme (4) is Phase II–dominant — the stress-granule program is most active in cells under chronic inflammatory stress, and the conversion of granules to aggregates occurs principally

in the microglial-recruitment phase. None of the five themes is purely Phase III; the matrix-degradation and PV+ -interneuron biology that defines Phase III is not appreciably implicated by the Mendelian architecture. This is itself an important observation: the Phase III biology is genetically encoded almost entirely in the common-variant architecture, which is why the field discovered it only after the GWAS era, and why the matrix-degradation literature has remained partially disconnected from the Mendelian literature for so long.

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4. Chapter II — APOE: The Master Variable and Its Three-Phase Mechanism

4.1 Allelic Structure and Effect Sizes

APOE (chromosome 19q13.32) encodes apolipoprotein E, a 299-residue glycoprotein synthesized principally by hepatocytes in the periphery and by astrocytes (and, to a lesser extent, microglia and stressed neurons) in the brain. The gene carries three common alleles — *APOE2* (cysteine at residues 112 and 158), *APOE3* (cysteine 112, arginine 158), and *APOE4* (arginine at both 112 and 158) — at population frequencies of approximately 7%, 78%, and 14% in Europeans. The single amino-acid difference at residue 112 reorganizes the protein's tertiary structure, with consequences for lipid binding, receptor affinity, and cellular trafficking that have made *APOE* the single best-characterized common-variant gene in human disease genetics.

The effect of *APOE* on Alzheimer's disease risk is unique in its magnitude. Heterozygous *APOE4* carriers (population frequency ~25%) carry an odds ratio of approximately 3.0 for late-onset AD; homozygous *APOE4/4* carriers (population frequency ~2–3%) carry an odds ratio of approximately 12–14 (Corder et al., 1993; Farrer et al., 1997; Genin et al., 2011; Reiman et al., 2020; Fortea et al., 2024). Each *APOE4* allele advances the median age of onset by approximately 5–7 years; each *APOE2* allele delays it by approximately 3–4 years. The 2024 demonstration by Fortea et al. that *APOE4/4* homozygotes constitute a near-Mendelian form of AD — with virtually complete penetrance of AD pathology by age 75 and clinical symptoms by age 80 — has reorganized the conventional understanding of *APOE* from a polygenic risk factor into a high-penetrance genetic disease in its own right, with implications for screening, counseling, and trial enrollment that the field is still

working out.

The mechanistic question — *why* APOE4 confers risk — has resisted resolution despite three decades of work, and the resistance is itself diagnostic. APOE4 differs from APOE3 by a single amino-acid substitution, but the cellular consequences of that substitution are not localized to a single biochemical step. APOE4 alters lipid binding, receptor affinity, intracellular trafficking, microglial activation, astrocyte cholesterol homeostasis, blood-brain-barrier integrity, neuronal Aβ uptake, tau phosphorylation, and synaptic pruning. The reason no single mechanism has been resolved is that all of them are real, and the gene's effect is the sum of contributions across phases.

4.2 APOE in Phase I — Lipid Handling and Bioenergetic Coupling

The Phase I contribution of APOE is principally to the brain's lipid economy. Cholesterol is required for membrane synthesis, myelin maintenance, and synapse formation, but cannot cross the blood-brain barrier; the brain synthesizes its own cholesterol locally, principally in astrocytes, and distributes it to neurons and oligodendrocytes via lipoprotein particles whose principal apolipoprotein is APOE. APOE4-containing particles bind lipid less efficiently and are degraded faster than APOE3-containing particles, with the consequence that astrocyte-to-neuron cholesterol delivery is reduced in APOE4 carriers (Wang et al., 2021; Blanchard et al., 2022). The reduced cholesterol delivery has bioenergetic consequences — myelin maintenance, mitochondrial membrane integrity, and the synthesis of phosphatidylethanolamine and cardiolipin that the mitochondria require for cristae assembly are all impaired — and these consequences are most consequential in the highest-energy-demand projection neurons, including the locus coeruleus, the dorsal raphe, and the basal forebrain cholinergic neurons that define the Phase I anatomy.

APOE4 also produces direct mitochondrial dysfunction in iPSC-derived neurons, with reduced complex IV activity, reduced membrane potential, and increased reactive oxygen species (Orr et al., 2019; Tambini et al., 2016). The mechanism couples APOE4-driven lipid mishandling to mitochondrial-membrane-associated mitochondria (MAM) signaling — the same MAM compartment in which Area-Gomez and colleagues have characterized PSEN1-driven dysfunction — and supplies a direct molecular link between the APOE and PSEN1 axes at the Phase I substrate level.

4.3 APOE in Phase II — Microglial State and Lipid Droplet Accumulation

The Phase II contribution of APOE is principally to microglial state. APOE is the single most upregulated gene in disease-associated microglia (DAM) in the mouse 5xFAD model and in human postmortem AD brain (Keren-Shaul et al., 2017; Mathys et al., 2019), and the APOE-positive microglial state is functionally and transcriptionally distinct from the homeostatic state. APOE4 carriers show enhanced microglial activation, increased complement deposition, and elevated cytokine production at every age examined (Shi et al., 2017; Liu et al., 2017), with the consequence that the entry into Phase II microglial recruitment is accelerated in APOE4 carriers by years to decades.

The most recently characterized Phase II contribution of APOE is to the lipid-droplet-accumulating microglia (LDAM) phenotype identified by Marschallinger et al. (2020) and elaborated in the subsequent literature (Aske et al., manuscript; Haney et al., 2024). LDAM are microglia whose cytoplasm is occupied by large neutral-lipid droplets, whose phagocytic capacity is reduced, and whose secretome is pro-inflammatory. APOE4 carriers show a dramatically expanded LDAM population in aged brain, with the lipid composition of the droplets matching the lipid signatures of APOE4-driven cholesterol mishandling (Haney et al., 2024). The LDAM phenotype is therefore the Phase II terminus of the Phase I lipid-handling defect, and it supplies a direct molecular mechanism for the way APOE4 carriers cross from Phase I into Phase II faster than APOE3 carriers.

4.4 APOE in Phase III — Perineuronal Nets and Synaptic Pruning

The Phase III contribution of APOE has received less attention but is now well-supported. APOE is expressed by perineuronal-net-ensheathed parvalbumin interneurons under conditions of stress (Lewandowski et al., 2024; Crapser et al., 2020), and APOE4 carriers show accelerated PNN loss in postmortem cortex and in mouse models (Crapser et al., 2020). The mechanism couples APOE4 to microglial-driven complement deposition on PV+ synapses (the C1q–C3 axis characterized by Stevens, Schafer, and colleagues; Hong et al., 2016) and to the MMP-9-driven matrix degradation that defines the Phase III collapse. APOE4 carriers also show enhanced complement activity in CSF (Tijms et al., 2024) and altered C1q expression in microglia, supplying a direct Phase III mechanism that operates through the same complement axis as the rest of the matrix biology.

The three-phase mechanism of APOE is therefore not a single mechanism applied across three phases but three distinct mechanisms — lipid mishandling in Phase I, microglial-state and LDAM in Phase II, and complement-mediated PNN attack in Phase III — each load-bearing in its own phase and each compounding the others. This is the architectural feature that makes APOE the master variable: not that it has a large effect at any single locus, but that it has a moderate effect at three loci that happen to align with the three phases. The cumulative effect across the life course is the product of the per-phase effects, which is why the homozygous-carrier risk is multiplicative, not additive.

4.5 APOE Christchurch and Other Protective Variants

The 2019 report of the *APOE3* Christchurch homozygous carrier (R136S) in the Colombian PSEN1 E280A kindred (Arboleda-Velasquez et al., 2019) is the single most important recent finding in APOE biology. The carrier, who had two copies of the PSEN1 E280A mutation and would have been expected to develop EOAD by age 45, remained cognitively intact into her 70s despite massive amyloid deposition. The protective variant maps to the heparan-sulfate-proteoglycan-binding interface of APOE and reduces APOE's binding to HSPGs; the proposed mechanism is that reduced HSPG binding reduces tau spread, complement activation, and microglial pro-inflammatory signaling. The Christchurch variant thus identifies the *APOE–HSPG–tau* axis as a load-bearing Phase II and Phase III mechanism and supplies a therapeutic surface — the development of HSPG-binding-mimetic peptides that recapitulate the Christchurch effect — that is now being actively pursued.

The 2023 RELN-COLBOS report (Lopera et al., 2023) identified a second protective variant in a heterozygous male carrier of the same E280A mutation, this time in *RELN* (the gene encoding reelin, the ligand of the ApoER2/VLDLR lipoprotein receptors that also carry APOE). Rather than acting through a mechanism wholly separate from Christchurch, the two variants converge on a shared molecular node — the heparan-sulfate-dependent signaling of the ApoER2/VLDLR lipoprotein receptors. The Christchurch variant *loosens* APOE's pathological binding to heparan sulfate, whereas the COLBOS variant *tightens* reelin's protective binding to the same co-receptor, strengthening reelin□Dab1 signaling and its brake on tau (Pan et al., 2025). Both thereby spare the entorhinal cortex from tau even as amyloid accumulation proceeds unimpeded — a Phase III protective effect, operating on the same lipoprotein-receptor axis from opposite ligands, that further validates the temporal-phase framework. (The reelin arm of this convergence is developed in full in the companion monograph *The Architect's Reprieve*.)

5. Chapter III — The Phase I Genome: Bioenergetic, Mitochondrial, and Locus-Coeruleus Genes

5.1 The NAD□ Metabolic Network

NAD□ (nicotinamide adenine dinucleotide) is the cofactor whose depletion organizes Phase I. NAD□ is required for oxidative phosphorylation (as the electron acceptor at complex I), for the sirtuin deacetylases (SIRT1–7), for the PARP family (PARP1–17), for the CD38/CD157 NAD glycohydrolases, and for SARM1 (the executioner of programmed axonal degeneration). The cofactor is synthesized through three pathways: the salvage pathway (the dominant pathway in most tissues, recycling nicotinamide via NAMPT and NMNAT), the Preiss–Handler pathway (incorporating dietary niacin via NAPRT and NMNAT), and the de novo pathway (synthesizing NAD□ from tryptophan via the kynurenine cascade, as elaborated in the companion volume on the tryptophan partition).

NMNAT2 (chromosome 1q25.3) encodes the nicotinamide mononucleotide adenylyltransferase isoform that supplies NAD□ to axons. NMNAT2 has a short half-life (~4 hours) and must be continuously delivered to distal axons by anterograde axonal transport; any interruption of transport — by mitochondrial failure, microtubule destabilization, or simple axonal injury — depletes NMNAT2 distal to the interruption, NAD□ falls, and NMN (nicotinamide mononucleotide) accumulates. The NMN accumulation activates SARM1.

SARM1 (chromosome 17q11.2) encodes a TIR-domain NADase whose activation triggers a catastrophic intra-axonal NAD□ collapse and committed axonal degeneration (Gerdts et al., 2015; Essuman et al., 2017). SARM1 is an allosteric enzyme that is autoinhibited by NAD□ and activated by NMN; the NMN:NAD□ ratio is therefore the load-bearing signal that determines whether an axon survives or executes the Wallerian-like degeneration program. Heterozygous SARM1 gain-of-function variants are associated with ALS (Bloom et al., 2022), and SARM1 inhibition is in active clinical development as a strategy to protect axons in ALS, peripheral neuropathy, chemotherapy-induced neuropathy, and diabetic neuropathy. In the context of the Phase I framework, SARM1 is the executioner of the long-axon vulnerability that characterizes locus coeruleus neurons — cells whose long, thin, unmyelinated or sparsely myelinated projections (Braak et al., 2006) carry a high cumulative NAD□ demand along their length. The magnitude of that demand should

not be overstated. No published estimate of total axonal length per human locus coeruleus neuron exists; the quantified arbor-burden calculation available in the literature is for substantia nigra dopamine neurons (Pissadaki and Bolam, 2013), whose geometry is not transferable to the coeruleus. What the coerulean evidence does establish is a vulnerability of axonal *architecture* — length, thinness, and absent myelination — rather than a measured arbor size.

NAMPT (chromosome 7q22.3) encodes nicotinamide phosphoribosyltransferase, the rate-limiting enzyme of the NAD□ salvage pathway. NAMPT expression declines with age in multiple tissues including brain, and the decline is a load-bearing cause of the age-associated drop in cellular NAD□ (Camacho-Pereira et al., 2016; Zhu et al., 2015). NAMPT is the principal source of NAD□ supply that compensates for the inflammation-driven NAD□ demand from PARP1 activation, and its decline in aging therefore tightens the bioenergetic constraint that drives Phase I.

CD38 (chromosome 4p15.32) encodes a transmembrane NAD glycohydrolase that consumes NAD□ to generate cyclic ADP-ribose (and, at much lower levels, NAADP). CD38 is upregulated on activated microglia and macrophages and is the principal cellular sink for NAD□ in the aged brain (Camacho-Pereira et al., 2016; Chini et al., 2020; Tarragó et al., 2018). The age-associated rise in CD38 expression on inflammatory cells is mechanistically coupled to the age-associated fall in NAD□ — CD38 is the demand-side counterpart to the supply-side decline of NAMPT — and CD38 inhibition (78c, apigenin, luteolinidin) has emerged as a therapeutic strategy to raise tissue NAD□ without exogenous precursor administration.

NMRK1 (chromosome 9q21.13) and *NMRK2* (chromosome 19p13.3) encode nicotinamide riboside kinases that incorporate exogenous nicotinamide riboside (the leading clinical NAD□ precursor) into the salvage pathway. ATF4-driven upregulation of NMRK1 under stress (Mungrue et al., 2009) couples NR utilization to the integrated stress response and supplies the molecular basis for the observation that the NAD□-elevating effects of NR are largest in tissues under bioenergetic stress.

The sirtuin family (*SIRT1–SIRT7*) encodes seven NAD□-dependent deacetylases with distinct subcellular localizations (SIRT1, SIRT6, SIRT7 nuclear; SIRT2 cytoplasmic; SIRT3, SIRT4, SIRT5 mitochondrial). SIRT1 deacetylates PGC-1α (the master regulator of mitochondrial biogenesis), p53, FOXO transcription factors, and the autophagy proteins; SIRT3 deacetylates SOD2, IDH2, and the OXPHOS

complexes. Sirtuin activity is exquisitely sensitive to NAD□ availability — the Km of SIRT1 for NAD□ is ~150 μM, which is within the range of cellular NAD□ fluctuation — and the activity decline that accompanies NAD□ depletion is therefore a direct functional consequence of the upstream metabolic constraint.

5.2 Mitochondrial Quality Control

The Phase I mitochondrial-quality-control machinery is anchored by the PINK1–Parkin mitophagy axis (treated in §3.3) and extended by a set of genes whose mutations and common variants modulate mitochondrial dynamics, biogenesis, and turnover.

OPA1 (chromosome 3q29) encodes the dynamin-like GTPase of the mitochondrial inner membrane that controls cristae morphology and inner-membrane fusion. *OPA1* mutations cause dominant optic atrophy with the most prominent vulnerability in retinal ganglion cells, whose long axons share the bioenergetic vulnerability of locus coeruleus neurons. *MFN1* and *MFN2* (chromosomes 3q26.33 and 1p36.22) encode the outer-membrane mitofusins; *MFN2* mutations cause Charcot-Marie-Tooth type 2A through similar long-axon vulnerability. *DRP1/DNM1L* (chromosome 12p11.21) encodes the dynamin-related GTPase that drives mitochondrial fission, and its dysregulation in AD has been characterized by Reddy and colleagues (Manczak et al., 2011, 2018). The fusion/fission balance is itself a quality-control mechanism: fusion mixes mitochondrial contents and averages out individual organelle damage, while fission segregates damaged subunits for mitophagy, and the balance is set by signals (membrane potential, calcium, ROS) that feed back to the inner- and outer-membrane fission/fusion machinery.

POLG (chromosome 15q26.1) encodes mitochondrial DNA polymerase γ, the only polymerase that replicates mtDNA. *POLG* mutations cause a spectrum of mitochondrial disease ranging from Alpers' syndrome to progressive external ophthalmoplegia to early-onset parkinsonism (Luoma et al., 2004), and mtDNA mutations accumulate with age in dopaminergic and noradrenergic neurons (Bender et al., 2006; Kraytsberg et al., 2006), supplying a Phase I substrate-level mechanism for the gradual decline of mitochondrial function in projection neurons.

TFAM (chromosome 10q21.1) encodes mitochondrial transcription factor A, the principal nucleoid-organizing protein of mtDNA. TFAM levels set the mtDNA copy

number and the rate of mitochondrial biogenesis; its expression is regulated by PGC-1α, NRF1, and NRF2, all of which decline with age. The TFAM-PGC-1α axis is the load-bearing transcriptional axis of mitochondrial biogenesis and is the principal compensatory pathway against the Phase I substrate constraint.

The mitochondrial-targeted antioxidants — superoxide dismutase 2 (*SOD2*), glutathione peroxidase 1 (*GPX1*), thioredoxin 2 (*TXN2*) — supply the defensive machinery against the ROS generated by leaky electron transport. SOD2 deficiency in mice produces a phenotype dominated by cardiomyopathy and neurodegeneration; common-variant signals near *SOD2* and the mitochondrial antioxidants have not reached genome-wide significance in AD GWAS but are robust modifiers of mitochondrial-disease phenotypes.

5.3 The Autophagy–Lysosomal Machinery

TFEB (chromosome 6p21.1) is the master transcriptional regulator of autophagy and lysosomal biogenesis. TFEB is normally phosphorylated by mTORC1 at the lysosomal surface, sequestered in the cytoplasm, and inactive; on starvation, lysosomal stress, or mitochondrial dysfunction, mTORC1 is inhibited, TFEB is dephosphorylated by calcineurin, and translocates to the nucleus where it activates the CLEAR network (Coordinated Lysosomal Expression and Regulation) — a coordinated transcriptional program of ~500 genes encoding lysosomal enzymes, the V-ATPase subunits, the autophagy machinery, and the lysosomal biogenesis program (Sardiello et al., 2009; Settembre et al., 2011, 2012). TFEB activity is the principal cellular response to bioenergetic stress, and its progressive impairment in AD postmortem brain (Wang et al., 2016; Polito et al., 2014) is one of the load-bearing Phase I mechanisms. *TFE3* (chromosome Xp11.23) is the paralog that performs a parallel function in cell types where TFEB is less abundant.

ATG7 (chromosome 3p25.3), *BECN1* (chromosome 17q21.31), *ATG5* (chromosome 6q21), and *MAP1LC3B* (chromosome 16q24.2) encode the core autophagy machinery. Neuron-specific knockouts of *Atg7* or *Atg5* in mice produce widespread neurodegeneration (Komatsu et al., 2006; Hara et al., 2006), establishing autophagy as constitutively required for neuronal survival.

The selective-autophagy adapters — *OPTN* (optineurin, chromosome 10p13), *NDP52/CALCOCO2* (chromosome 17q21.32), *TAX1BP1* (chromosome 7p15.2), and *SQSTM1/p62* (chromosome 5q35.3) — couple ubiquitinated cargo (damaged

mitochondria, aggregated protein, intracellular pathogens) to the autophagy machinery through LC3-binding motifs. *OPTN* and *SQSTM1* mutations cause ALS-FTD, and *OPTN* loss compromises mitophagy. The genetic architecture of selective autophagy locates a substantial fraction of the Phase I biology in the convergent ALS-PD-FTD-AD overlap zone and supplies the molecular basis for the cross-disease pathway convergence.

The v-ATPase subunits — *ATP6V0A1* (chromosome 17q21.2) and the broader v-ATPase family — supply the lysosomal acidification that lysosomal proteases require. Lysosomal acidification failure has been characterized as a load-bearing Phase I mechanism (Lee et al., 2022; Nixon, 2020; Mindell, 2012), with the v-ATPase functioning as the bridge between mitochondrial ATP supply and lysosomal proteolytic capacity. The convergence of mitochondrial dysfunction (Phase I) on lysosomal failure (Phase I) through v-ATPase ATP-dependence is one of the most direct molecular couplings in the framework.

5.4 The Integrated Stress Response

The integrated stress response (ISR) is the cellular program that converts diverse stress signals — amino-acid starvation, ER stress, viral infection, oxidative stress, heme deficiency — into a unified translational response through the phosphorylation of eIF2α at serine 51. Four eIF2α kinases — *EIF2AK1/HRI* (heme), *EIF2AK2/PKR* (viral dsRNA), *EIF2AK3/PERK* (ER stress), *EIF2AK4/GCN2* (amino-acid starvation) — supply input-specific sensing, all converging on the same downstream eIF2α phosphorylation and the same downstream activation of *ATF4* (Costa-Mattioli and Walter, 2020; Pakos-Zebrucka et al., 2016).

ATF4 (chromosome 22q13.1) is the master transcription factor of the ISR. Its translation is actively repressed under homeostatic conditions and de-repressed under eIF2α phosphorylation. ATF4 upregulates the amino-acid biosynthesis genes (including the kynurenine-pathway enzymes, treated in the tryptophan-partition companion volume), the NAD□-salvage genes (NAMPT, NMRK1), the autophagy machinery (ATG5, ATG7, MAP1LC3B, p62), and — critically — its own apoptotic-branch executor *CHOP/DDIT3* (chromosome 12q13.3). CHOP drives apoptotic gene expression when the ISR fails to resolve and is the molecular switch that converts a protective stress response into a death program. *GADD34/PPP1R15A* (chromosome 19q13.33) is the phosphatase that dephosphorylates eIF2α and

resolves the ISR; its CHOP-driven upregulation supplies the negative feedback that allows the ISR to terminate, and its dysregulation produces the chronic-ISR state that has been characterized in AD postmortem brain (Hetz and Saxena, 2017; Hwang et al., 2022).

The ISR's centrality to neurodegeneration has been most rigorously demonstrated by the work of Costa-Mattioli, Walter, and colleagues, who showed that ISRIB (a small-molecule inhibitor of the ISR that selectively reverses the eIF2α-driven translational block) restores synaptic plasticity, memory, and cognitive function in multiple AD, ALS, FTD, and TBI mouse models (Sidrauski et al., 2015; Halliday et al., 2015; Chou et al., 2017; Wong et al., 2019). The ISR is therefore a load-bearing Phase I mechanism whose pharmacological reversal is now in active clinical development.

5.5 The Locus Coeruleus Identity Program

The locus coeruleus (LC) is the noradrenergic projection nucleus whose pre-symptomatic pathology (Braak stages 0–II) is now understood as the anatomical anchor of Phase I (Mather and Harley, 2016; Weinshenker, 2018; Kelberman et al., 2024). The LC is small — on the order of twenty thousand neurons per side counted as tyrosine-hydroxylase-positive, neuromelanin-bearing cells (Manaye et al., 1995), or nearer fifty thousand per side counted inclusively (Theofilas et al., 2017) — its neurons are projecting, sending long, thin, sparsely myelinated axons across the forebrain, and they synthesize and release norepinephrine to virtually every cortical region. The LC identity program comprises a small set of transcription factors and metabolic enzymes that, when disrupted, are catastrophic for the LC even if they are tolerable elsewhere.

TH (chromosome 11p15.5) encodes tyrosine hydroxylase, the rate-limiting enzyme of catecholamine biosynthesis. TH converts L-tyrosine to L-DOPA and is regulated at the level of phosphorylation, protein stability, and BH4 cofactor availability. The continuous catecholamine synthesis required for LC function imposes a substantial bioenergetic load — tyrosine hydroxylation requires molecular oxygen and BH4, generating dopamine that must subsequently be hydroxylated by DBH and packaged into VMAT2-positive vesicles. *DBH* (chromosome 9q34.2) encodes dopamine β-hydroxylase, the LC-specific enzyme that converts dopamine to norepinephrine and the only enzyme in the catecholamine cascade that is restricted

to noradrenergic neurons. *SLC18A2* (chromosome 10q25.3) encodes VMAT2, the vesicular monoamine transporter that loads catecholamines into synaptic vesicles; VMAT2 loss exposes cytoplasmic dopamine and norepinephrine to monoamine-oxidase-driven oxidation, generating reactive aldehyde intermediates that are themselves substrates for the LC's age-associated oxidative burden (Lohr et al., 2014; Goldstein et al., 2013).

The LC's vulnerability to MAO-driven oxidation, combined with its dependence on continuous BH4 supply (which is itself sensitive to ISR-driven GTP cyclohydrolase regulation), its NAD□-demanding axonal arbor (which makes it the principal substrate of SARM1 vulnerability), and its mitochondrial complex I dependence (which exposes it to the bioenergetic constraint that organizes Phase I), makes it the single most vulnerable projection-neuron population in the human brain and the anatomical anchor of Phase I.

5.6 The Tryptophan-Partition Genes (Brief Treatment)

The tryptophan-partition genes — *IDO1*, *IDO2*, *TDO2*, *KMO*, *KYNU*, *KAT1–KAT4*, *QPRT*, *TPH1*, *TPH2*, *DDC* — are treated in detail in the companion dissertation, *The Tryptophan Partition*. For the purposes of the present chapter, it is sufficient to note that these genes encode the catabolic enzymes whose differential regulation under inflammation and stress determines how the brain's tryptophan supply is allocated across the kynurenine, NAD□, serotonergic, and tryptamine branches, and that the *KMO*, *KYNU*, and *QPRT* genes are particularly implicated in the Phase I bioenergetic biology through their role in de novo NAD□ synthesis from quinolinic acid.

6. Chapter IV — The Phase II Genome: Microglial, Complement, Ferroptosis, and Oligodendroglial Genes

6.1 TREM2 and the TYROBP–DAP12 Adapter

TREM2 (triggering receptor expressed on myeloid cells 2; chromosome 6p21.1) encodes a single-pass transmembrane receptor expressed on microglia, macrophages, and a subset of dendritic cells. TREM2 signals through the immunoreceptor-tyrosine-based-activation-motif (ITAM)-containing adapter *TYROBP/DAP12* (chromosome 19q13.12), which on TREM2 engagement recruits SYK kinase, which in turn activates PLCγ2, PI3K, and the downstream signaling cascade that drives microglial migration, phagocytosis, proliferation, and the disease-associated microglial state.

The TREM2 R47H variant (rs75932628) was identified independently by Guerreiro et al. (2013) and Jonsson et al. (2013) as a rare missense variant with a heterozygous odds ratio of approximately 3.0 for late-onset AD — a magnitude approaching APOE4 heterozygote risk. The variant impairs TREM2 binding to its lipid and Aβ ligands, reduces microglial recruitment to plaques, and shifts the microglial transcriptional state away from the DAM signature (Wang et al., 2015; Yuan et al., 2016). The implication is that the protective response to amyloid accumulation — the microglial encapsulation, processing, and clearance of plaques — is impaired in R47H carriers, and that this impairment is sufficient to elevate disease risk by a factor of three.

The discovery of TREM2 R47H reorganized the AD field's understanding of microglia from a passive bystander to an active participant in disease pathogenesis. Together with the GWAS-identified TREM2 common-variant signal and with the broader literature on TREM2 in lipid handling and aging (Ulland et al., 2017; Ulland and Colonna, 2018; Nugent et al., 2020), TREM2 has emerged as the single most actively pursued microglial therapeutic target, with multiple TREM2-agonist antibodies in clinical trials.

6.2 The CD33 and MS4A Clusters

CD33/SIGLEC3 (chromosome 19q13.41) encodes a sialic-acid-binding immunoglobulin-like lectin expressed on microglia that, on engagement, recruits SHP1/SHP2 phosphatases and inhibits microglial activation and phagocytosis. The CD33 GWAS signal in AD (Hollingworth et al., 2011; Naj et al., 2011) acts through an exon-2 splicing variant (rs12459419) that controls the inclusion of the sialic-acid-binding V-set domain; the protective allele increases inclusion of a CD33 isoform that lacks the inhibitory function and therefore promotes microglial phagocytosis. The CD33 mechanism is the inverse of the TREM2 mechanism — TREM2 loss-of-function impairs microglial activation, CD33 loss-of-function enhances it — and both converge on the same Phase II microglial-recruitment biology.

The *MS4A* cluster (chromosome 11q12.2) contains the genes encoding several members of the four-membrane-spanning protein family that participate in immune-cell signaling (the most familiar being MS4A1/CD20 on B cells). In AD, the principal signals are at *MS4A4A*, *MS4A6A*, and *MS4A4E* (Hollingworth et al., 2011; Naj et al., 2011; Deming et al., 2019). The functional impact of the cluster has been clarified by the demonstration that MS4A4A modulates soluble TREM2 levels in CSF (Deming et al., 2019), couples the cluster directly to the TREM2 axis, and makes MS4A4A a candidate biomarker and therapeutic target.

6.3 PLCG2, ABI3, INPP5D, MEF2C, SPI1

The 2017 paper by Sims et al. identified rare coding variants in *PLCG2* and *ABI3* as AD risk modifiers, with the *PLCG2* P522R variant carrying a protective odds ratio of ~0.7 and the *ABI3* S209F variant carrying a small risk effect. *PLCG2* (chromosome 16q23.3) encodes phospholipase Cγ2, the downstream effector of TREM2 signaling; the P522R variant produces a hyperactive PLCγ2 with enhanced PIP2 hydrolysis and consequently enhanced microglial responsiveness (Magno et al., 2019). The P522R protective effect is currently the best-characterized example of a "gain-of-function-of-microglia" protective variant, and it identifies the TREM2–PLCG2 axis as a therapeutic surface where receptor agonism would be expected to recapitulate the genetic protection.

ABI3 (chromosome 17q21.32) encodes ABI family member 3, a microglial cytoskeletal regulator of the WAVE2 complex; its variants likely modulate microglial

migration and process dynamics. *INPP5D* (chromosome 2q37.1) encodes SHIP1, a phosphoinositide 5-phosphatase that opposes PI3K signaling in microglia and downregulates the TREM2-driven activation program; its risk variants are presumed loss-of-function, consistent with the broader pattern that the AD GWAS architecture identifies risk variants that constrain microglial responsiveness.

MEF2C (chromosome 5q14.3) encodes myocyte enhancer factor 2C, a transcription factor with dual roles in microglial homeostasis and in neuronal late-stage development; its loss is associated with both microglial activation and synaptic dysfunction (Deczkowska et al., 2017). *SPI1/PU.1* (chromosome 11p11.2) is the myeloid master transcription factor that establishes microglial identity from the yolk-sac myeloid lineage; its common-variant signal in AD modulates SPI1 expression in microglia and shifts the homeostatic-DAM balance toward DAM (Huang et al., 2017).

6.4 The Complement Axis

The complement system supplies the molecular machinery of microglial synaptic pruning, which is the principal mechanism by which microglia execute the synaptic loss that defines the Phase II transition (Stevens et al., 2007; Schafer et al., 2012; Hong et al., 2016; Lui et al., 2016). The classical complement cascade — *C1QA*, *C1QB*, *C1QC* (chromosome 1p36.12), *C2* (chromosome 6p21.32), *C3* (chromosome 19p13.3), *C4A*/*C4B* (chromosome 6p21.33) — deposits opsonization tags on synapses that microglial *CR3/ITGAM* (CD11b/CD18) and *CR1* (chromosome 1q32.2) receptors recognize and phagocytose. The C1q–C3–CR3 axis is normally restricted to developmental synaptic pruning, where it operates in the late embryonic and early postnatal CNS to refine synaptic connectivity. In neurodegeneration, the axis is re-activated, with C1q deposition appearing on synapses years before clinical symptoms (Hong et al., 2016) and microglial-driven synaptic engulfment correlating spatially with cognitive decline.

The *CR1* AD GWAS signal (Lambert et al., 2009; Hollingworth et al., 2011) is one of the earliest and most replicated common-variant signals in AD. *C4A* common-variant signals associated with schizophrenia (Sekar et al., 2016) supply a parallel example of the complement-pruning axis driving brain disorder. The complement-targeted therapeutic strategies — most notably the anti-C1q antibody ANX005/ANX007 from Annexon Biosciences, currently in clinical trials for ALS, AD,

and geographic atrophy — are based on this Phase II mechanism.

6.5 The Homeostatic-Microglial Identity Program

The homeostatic microglial identity program is anchored by a transcriptional network that includes *SALL1* (chromosome 16q12.1), *MEF2C*, *EGR1*, *MAFB*, *SMAD3*, and the TGF-β receptor genes *TGFBR1* (chromosome 9q22.33) and *TGFBR2* (chromosome 3p24.1). TGF-β signaling, originating from neurons, astrocytes, and microglia themselves, is the principal extrinsic signal that maintains the homeostatic microglial state (Butovsky et al., 2014; Buttgereit et al., 2016; Spittau et al., 2020); its loss precipitates the transition to DAM and the loss of the homeostatic markers *P2RY12*, *P2RY13* (chromosome 3q25.1), *TMEM119* (chromosome 12q24.31), *CX3CR1* (chromosome 3p22.2), and *SLC2A5*.

The Phase II transition is therefore most precisely described as the loss of TGF-β-driven homeostatic identity, with the disease-associated state emerging by default once the homeostatic program is no longer maintained. Restoring TGF-β signaling — through receptor agonism, downstream SMAD3 activation, or upstream cytokine supplementation — has been proposed as a Phase II therapeutic strategy (Schwartz et al., 2024), and the framework predicts that such interventions would be most effective when applied during the Phase II transition, before microglial-state collapse has fully consolidated.

6.6 The Ferroptosis Defense Machinery

Ferroptosis is an iron-dependent lipid-peroxidation-driven form of regulated cell death (Dixon et al., 2012; Stockwell et al., 2017) whose principal substrate in the brain is the polyunsaturated-fatty-acid-rich oligodendrocyte. The defense against ferroptosis is anchored by *GPX4* (chromosome 19p13.3), the selenocysteine-containing glutathione peroxidase that reduces lipid hydroperoxides to lipid alcohols; GPX4 loss is the most direct cellular trigger of ferroptosis. *FSP1/AIFM2* (chromosome 10q22.1) encodes ferroptosis-suppressor protein 1, the CoQ10-reducing alternative defense pathway identified by Doll et al. (2019) and Bersuker et al. (2019). *NFE2L2/NRF2* (chromosome 2q31.2) is the master antioxidant transcription factor whose targets include *SLC7A11* (chromosome 4q28.3, the cystine-glutamate antiporter that supplies cysteine for glutathione synthesis), *GCLC* (chromosome 6p12.1, the rate-limiting glutathione-synthesis enzyme), and the ferritin genes. The NRF2-driven antioxidant program supplies the principal compensatory response against ferroptotic stress, and its progressive impairment with age is one of the load-bearing Phase II vulnerabilities.

The ferroptosis execution program — *ACSL4* (chromosome 11q22.3, the acyl-CoA synthetase that activates PUFA for membrane incorporation), *LPCAT3* (chromosome 1p13.3, the lysophospholipid acyltransferase that incorporates PUFA into membrane phospholipids), *ALOX15* (chromosome 17p13.2, the 15-lipoxygenase that peroxidizes PUFA), and *ALOX5* — supplies the molecular machinery of the death itself. Pharmacological inhibition at any of these nodes is sufficient to block ferroptosis, and the clinical-development pipeline of ferroptosis inhibitors (liproxstatin-1, ferrostatin-1, deferiprone, and several novel agents) is the principal therapeutic translation of the Phase II ferroptosis biology.

6.7 The Oligodendrocyte Identity Program

The oligodendrocyte identity program is anchored by *OLIG2* (chromosome 21q22.11), the master transcription factor of oligodendrocyte lineage commitment, and by the structural-myelin genes *MBP* (chromosome 18q23, myelin basic protein), *MOG* (chromosome 6p22.1, myelin oligodendrocyte glycoprotein), *PLP1* (chromosome Xq22.2, proteolipid protein 1, the most abundant myelin protein), and *MAG* (chromosome 19q13.12, myelin-associated glycoprotein). Oligodendrocyte loss in AD is one of the earliest cell-type-resolved findings in the single-cell era (Mathys et al., 2019; Pandey et al., 2022; Kenigsbuch et al., 2022), and the ferroptosis-vulnerability signatures of disease-associated oligodendrocytes locate the oligodendroglial loss directly within the Phase II framework.

The oligodendrocyte vulnerability is mechanistically explained by three factors: (1) the very high iron content of myelinating oligodendrocytes (which iron is required for the lipid-synthesis pathways that generate myelin lipids); (2) the very high PUFA content of myelin membranes (which makes them the most ferroptosis-vulnerable lipid compartment in the brain); and (3) the limited regenerative capacity of mature oligodendrocytes, which cannot easily replace themselves once lost.

6.8 ABCA7, ABCA1, CLU, PLD3

The lipid-handling axis of Phase II is anchored by the *APOE*-encoding apolipoprotein (Chapter II) and extended by several ATP-binding-cassette transporters and apolipoproteins. *ABCA7* (chromosome 19p13.3) is the third-largest AD GWAS hit and is functionally adjacent to ABCA1 in mediating cellular cholesterol and phospholipid efflux; rare loss-of-function variants confer substantial risk (Steinberg et al., 2015). *ABCA1* (chromosome 9q31.1) is the cholesterol-efflux pump that lipidates APOE; rare variants confer modest AD risk. *CLU/Apolipoprotein J* (chromosome 8p21.1) is the second-largest AD GWAS hit and encodes a chaperone-like apolipoprotein with extracellular Aβ-clearance activity. *PLD3* (chromosome 19q13.2) encodes phospholipase D3, a lysosomal enzyme whose rare coding variants confer late-onset AD risk through accumulation of undegraded lysosomal substrates and disruption of lipid metabolism.

6.9 The Phase II Synthesis

The Phase II genes describe a coherent system: a microglial sensor-and-effector network (TREM2, CD33, MS4A, PLCG2, ABI3, INPP5D, MEF2C, SPI1) that recognizes and clears damaged material; a complement axis (C1Q, C3, C4, CR1, CR3) that pre-tags the material for clearance; a homeostatic identity program (TGF-β, SALL1, P2RY12, CX3CR1) that constrains the activation; a ferroptosis-defense machinery (GPX4, FSP1, NRF2, SLC7A11) that protects the most vulnerable substrate (oligodendrocytes); an oligodendrocyte identity program (OLIG2, MBP, MOG, PLP1) that supplies the substrate itself; and a lipid-handling axis (APOE, ABCA7, ABCA1, CLU) that couples the system to the broader cholesterol economy. The system fails coherently — when one component degrades, the others compensate; when several degrade together, the system collapses; and the collapse is what we call the entry into Phase II.

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7. Chapter V — The Phase III Genome: Perineuronal-Net, Matrix, Parvalbumin, and Endocytic Genes

7.1 The Perineuronal-Net Structural Program

Perineuronal nets (PNNs) are dense lattice-like assemblies of chondroitin-sulfate proteoglycans (CSPGs), hyaluronan, and link proteins that ensheath the somata, dendrites, and proximal axons of approximately 5–10% of cortical neurons — predominantly the fast-spiking, parvalbumin-positive (PV+) inhibitory interneurons. PNNs supply mechanical, ionic, and biochemical scaffolding for the high-frequency firing that PV+ neurons execute and are the principal anatomical substrate of the Phase III collapse.

The PNN structural program is anchored by a small set of genes. *ACAN* (chromosome 15q26.1) encodes aggrecan, the largest and most abundant PNN CSPG. *BCAN* (chromosome 1q23.1) encodes brevican, the PV+-specific PNN CSPG whose role in PNN organization is now best characterized (Favuzzi et al., 2017). *NCAN* (chromosome 19p13.11) encodes neurocan and *VCAN* (chromosome 5q14.3) encodes versican; both contribute to the PNN core. *TNR* (chromosome 1q25.1) encodes tenascin R, the cross-linking glycoprotein that organizes the PNN lattice. *HAPLN1* (chromosome 5q14.3) and *HAPLN4* (chromosome 19p13.11) encode the

hyaluronan/proteoglycan link proteins that stabilize aggrecan-hyaluronan binding.

The PNN biosynthesis program comprises the hyaluronan synthases *HAS1*, *HAS2*, *HAS3* (chromosomes 19q13.41, 8q24.13, 16q22.1), the CSPG synthesis enzymes *CSGALNACT1* and *CSGALNACT2*, the sulfotransferases *CHST3* (chromosome 10q22.1, which sulfates CSPGs at the 6-position) and *CHST11* (chromosome 12q23.3, which sulfates at the 4-position), and the dual-functional epimerase-sulfotransferase *DSE* and *DSEL*. The 4-sulfate/6-sulfate ratio of CSPG sulfation is a load-bearing variable: 4-sulfated chondroitin (the developmental ratio) is permissive to plasticity, while 6-sulfated chondroitin (the adult ratio) is restrictive. Foscarin et al. (2017) and Miyata et al. (2018) showed that age-associated shifts in the 4/6 sulfation ratio reorganize the PNN's chemical character, and that the changes are reversible by enzymatic manipulation — supplying a chemical handle for PNN plasticity that is now in active therapeutic exploration.

7.2 The Matrix-Degradation Program: MMP-9, MMP-2, ADAMTS4, ADAMTS5

MMP9 (chromosome 20q13.12) encodes matrix metalloproteinase 9 (also gelatinase B), a zinc-dependent endopeptidase that degrades type-IV collagen, aggrecan, brevican, and several other PNN constituents. MMP-9 is secreted as a zymogen (proMMP-9) that requires activation by MMP-3 or by plasmin, and its activity is tightly opposed by the *TIMP* (tissue inhibitors of metalloproteinases) family — particularly *TIMP3* (chromosome 22q12.3), whose binding to MMP-9 produces an essentially irreversible inhibition. The MMP-9/TIMP-3 balance is the principal Phase III variable: when TIMP-3 is sufficient and MMP-9 is constrained, PNNs persist; when MMP-9 hyperactivity outstrips TIMP-3 supply, PNN aggrecan and brevican are progressively digested, the PV+ interneurons lose their plasticity-restricting matrix, gamma oscillations decline, and the cognitive trajectory enters the late-AD slope.

MMP2 (chromosome 16q12.2) encodes gelatinase A and supplies a parallel degradative capacity. *MMP3* (chromosome 11q22.2) is the activator of proMMP-9. *ADAMTS4* (chromosome 1q31.3) and *ADAMTS5* (chromosome 21q21.3) are the aggrecanases — disintegrin and metalloproteinase with thrombospondin motifs — whose cleavage of aggrecan generates the disease-associated fragment patterns that accumulate in AD CSF (Lemarchant et al., 2013).

The matrix-inhibitor program — *TIMP1* (chromosome Xp11.3), *TIMP2* (chromosome 17q25.3), *TIMP3*, and *RECK* (chromosome 9p13.3, the reversion-inducing cysteine-rich protein with kazal motifs) — supplies the load-bearing defense. *TIMP3* loss-of-function is the most direct Phase III genetic vulnerability characterized to date; the *TIMP3* Sorsby fundus dystrophy mutations supply the Mendelian anchor (Weber et al., 1994), and the common-variant TIMP3 signal in AD modulates expression in cortex and CSF.

7.3 The Parvalbumin-Interneuron Identity Program

The PV+ interneuron identity program is anchored by *PVALB* (chromosome 22q13.1), encoding the calcium-buffering protein that defines the cell type and supplies the fast calcium dynamics that high-frequency firing requires. The PV+ neurons express *GAD1* (chromosome 2q31.1, GAD67, the cytoplasmic GABA-synthesis enzyme) and *GAD2* (chromosome 10p12.1, GAD65, the vesicle-associated synaptic-GABA-synthesis enzyme), with the GAD1/GAD2 ratio shifted toward GAD1 in PV+ relative to other GABAergic populations. The PV+-specific membrane biophysics — the rapid kinetics of action-potential generation and the high-frequency firing capacity — depend on the Kv3-family potassium channels *KCNC1* (Kv3.1, chromosome 11p15.1), *KCNC2* (Kv3.2, chromosome 12q21.1), and *KCNC3* (Kv3.3, chromosome 19q13.33), whose unusually rapid deactivation kinetics permit the brief action potentials that PV+ neurons sustain.

The PV+ developmental and maintenance program is anchored by *LHX6* (chromosome 9q33.2), the LIM-homeodomain transcription factor that specifies the medial-ganglionic-eminence-derived interneurons; *NKX2-1* (chromosome 14q13.3), the upstream TF that defines the ventral telencephalon and specifies the broader PV+/SST interneuron lineage; and *ERBB4* (chromosome 2q34), the receptor tyrosine kinase that binds neuregulin-1 (*NRG1*, chromosome 8p12) and supplies the trophic signal that PV+ interneurons require for synaptic maturation and ongoing maintenance. *GPHN* (chromosome 14q23.3) encodes gephyrin, the postsynaptic scaffolding protein that clusters GABA-A receptors at inhibitory synapses; gephyrin loss compromises inhibitory transmission and is implicated in both autism and neurodegeneration.

The PV+ vulnerability is the central anatomical fact of Phase III: PV+ interneurons drive gamma oscillations (30–80 Hz), gamma oscillations gate hippocampal–cortical information flow, and PV+ loss therefore produces the network-level disorganization that defines clinical AD. The genetic architecture of Phase III is most informatively read as the architecture of PV+ vulnerability.

7.4 The Endocytic-Trafficking GWAS Axis

The fourth class of Phase III genes is the endocytic-trafficking axis, anchored by *BIN1*, *PICALM*, *SORL1*, *CD2AP*, and *EPHA1*. These genes have received less attention than the microglial GWAS hits because they are not as cleanly tied to a single cell type, but they are now understood to function in the synaptic compartment and to modulate the late-disease trajectory.

BIN1 (chromosome 2q14.3) is the second-largest AD GWAS hit after APOE. BIN1 encodes the bridging integrator 1 protein, a BAR-domain membrane-curvature-sensing protein that participates in clathrin-mediated endocytosis, tubular endosome biogenesis, and the trafficking of tau and AMPA receptors. BIN1's role in tau spread (Calafate et al., 2016) and in synaptic-vesicle endocytosis (De Rossi et al., 2016) locates it directly in the synaptic compartment of Phase III biology.

PICALM (chromosome 11q14.2) encodes phosphatidylinositol-binding clathrin assembly protein, a clathrin adaptor that participates in clathrin-mediated endocytosis at the synapse and at the blood-brain barrier (Zhao et al., 2015). The PICALM AD GWAS signal modulates Aβ clearance across the BBB and supplies a parallel mechanism to APOE for clearance impairment.

SORL1/LR11 (chromosome 11q24.1) encodes sortilin-related receptor 1, a member of the VPS10 receptor family that participates in retromer-mediated APP trafficking. Rare loss-of-function *SORL1* variants confer a substantial risk effect (~3-fold), positioning SORL1 as a borderline Mendelian AD gene and supplying a direct molecular link to the retromer biology that *VPS35* anchors in PD.

CD2AP (chromosome 6p12.3) encodes CD2-associated protein, a scaffold protein with roles in endocytic trafficking and in the maintenance of the blood-brain-barrier endothelial slit diaphragm. *EPHA1* (chromosome 7q34) encodes ephrin receptor A1, a receptor tyrosine kinase with roles in immune function and synaptic plasticity; its

functional contribution to AD is still being characterized.

7.5 The Synaptic-Scaffold Genes

A handful of synaptic-scaffold genes, while not principal GWAS hits in AD, are load-bearing for the Phase III biology. *DLG4* (chromosome 17p13.1) encodes PSD-95, the principal postsynaptic-density scaffolding protein that organizes NMDA and AMPA receptor clustering. *SHANK1*, *SHANK2*, *SHANK3* encode the SH3-ankyrin-repeat-domain proteins that organize the deeper postsynaptic density. The NMDA-receptor subunits *GRIN1*, *GRIN2A*, *GRIN2B*, *GRIN2C*, *GRIN2D* and the AMPA-receptor subunits *GRIA1–GRIA4* supply the principal excitatory channels whose dysregulation defines the late-AD synaptic phenotype. The synaptic-vesicle genes — *SYN1–SYN3*, *VAMP1–VAMP3*, *SNAP25*, *STX1A* — supply the release machinery.

7.6 The Phase III Synthesis

The Phase III genes describe a coherent system at higher resolution than has been previously assembled: a PNN structural program (ACAN, BCAN, TNR, HAPLN1) that supplies the matrix scaffolding; a CSPG-biosynthesis program (CSGALNACT, CHST3, CHST11, HAS3) that supplies the chemical composition; a matrix-degradation program (MMP9, MMP2, ADAMTS4/5) that supplies the proteolytic capacity; an inhibitor program (TIMP3, RECK) that constrains the proteolysis; a PV+-identity program (PVALB, GAD1/2, KCNC1-3, LHX6, ERBB4) that supplies the cellular substrate; an endocytic-trafficking axis (BIN1, PICALM, SORL1, CD2AP) that connects synaptic activity to membrane traffic; and a synaptic-scaffold program (DLG4, SHANK, GRIN, GRIA) that organizes the post-synaptic specialization. The Phase III collapse is the consequence of a coordinated failure across these subsystems, with MMP-9 hyperactivity over TIMP-3 supply as the load-bearing trigger and PV+ interneuron decompensation as the load-bearing consequence.

8. Chapter VI — Gene–Gene Interactions, Epistasis, and the Limits of Linear Polygenic Risk

8.1 APOE × TREM2

The interaction between APOE and TREM2 is the best-characterized epistatic interaction in AD genetics. APOE4 carriers with TREM2 R47H have AD risk substantially higher than the multiplicative product of the two individual effects would predict (Jin et al., 2014; Korvatska et al., 2015), consistent with a model in which the two genes act on the same biological substrate — microglial responsiveness to lipid-rich damage — and in which the loss of either component leaves the system unable to compensate. The mechanism couples APOE4-driven lipid mishandling (which increases the substrate that TREM2 must respond to) with TREM2 R47H impairment (which reduces the responsive capacity). The interaction makes biological sense within the phase framework: both genes contribute to the Phase II transition, and the joint impairment accelerates the transition by years rather than months.

8.2 APOE × ABCA7

The interaction between APOE and ABCA7 has been characterized as additive within the lipid-handling axis (Steinberg et al., 2015; De Roeck et al., 2019). Carriers of both an APOE4 allele and a rare ABCA7 loss-of-function variant exhibit risk substantially elevated above the APOE4 effect alone, with the interaction located in the cholesterol-efflux axis. Both genes act on the same lipid-substrate flux, and their joint impairment compromises the lipidated-APOE-particle supply that astrocytes deliver to neurons. The interaction is therefore principally a Phase I and Phase II interaction.

8.3 TREM2 × PLCG2

The interaction between TREM2 and PLCG2 is mechanistically obligate: PLCG2 is the immediate downstream effector of TREM2 signaling, and TREM2 R47H loss-of-function combined with PLCG2 P522R gain-of-function partially rescues the TREM2 R47H risk effect (Magno et al., 2019). The rescue is not complete, because the ligand-binding step (TREM2) and the signal-transduction step (PLCG2) are sequential rather than parallel, but the partial rescue is theoretically informative: it implies that pharmacological enhancement of the PLCG2 step downstream of impaired TREM2 receptor function might recapitulate the genetic-protection benefit, supplying a therapeutic strategy that does not require receptor agonism.

8.4 PSEN1 × APOE × RELN

The Colombian E280A PSEN1 kindred (Quiroz et al., 2018; Lopera et al., 2023) supplies the field's best-characterized example of a Mendelian gene whose effect is modified by both APOE Christchurch and RELN-COLBOS variants. The PSEN1 mutation produces autosomal-dominant EOAD with near-100% penetrance; the APOE Christchurch homozygote (Arboleda-Velasquez et al., 2019) delayed onset by 20+ years; the heterozygous RELN-COLBOS carrier (Lopera et al., 2023) delayed onset by a comparable interval. The two protective variants act on different ligands but converge on a shared effector node — the heparan-sulfate-dependent signaling of the ApoER2/VLDLR lipoprotein receptors. APOE Christchurch weakens APOE's pathological heparan-sulfate engagement (dampening tau spread and complement activation; Phase II/III), while RELN-COLBOS strengthens reelin's protective heparan-sulfate engagement (reinforcing the reelin□Dab1 brake on tau; Phase III); Pan et al. (2025) showed that heparan sulfate is the required co-receptor common to both. Their protection is therefore convergent rather than merely parallel — two ligands dialing the same receptor axis in opposite directions — which makes the pair one of the strongest pieces of human genetic evidence that the disease trajectory can be interrupted at this shared downstream node even when the upstream Mendelian driver (amyloid production) proceeds unimpeded.

8.5 The Polygenic-Risk-Score Problem

The conventional polygenic risk score (PRS) is constructed under a linear additive model: each genome-wide-significant SNP contributes its odds-ratio-weighted dosage to a single sum, and the sum is interpreted as overall disease risk. The model has the virtue of computational tractability and the vice of biological implausibility. The biology that the present dissertation has surveyed — three temporal phases, distinct gene sets per phase, with phase-spanning master variables and obligate epistatic interactions — predicts that the linear additive PRS systematically underestimates risk at the tail (where multiple high-risk alleles compound multiplicatively or super-multiplicatively) and overestimates risk in carriers whose risk is concentrated in a single phase that may not yet have been reached.

The phase-weighted PRS that the dissertation proposes is constructed as three sub-scores — Phase I PRS (the NAD□, mitochondrial, autophagy, ISR, and LC-identity gene loci); Phase II PRS (the microglial, complement, ferroptosis, oligodendroglial, and lipid-handling loci); Phase III PRS (the PNN, matrix, PV+ , and endocytic loci) — with the relative weights of the three sub-scores updated by the individual's biological-age estimate. The resulting profile says not how much total risk a person carries but how that risk is temporally distributed across the life course, and therefore which phase-specific interventions would be expected to be effective at which biological moment. The empirical validation of the phase-weighted PRS is in progress in the field; the framework anticipates that it will outperform the linear PRS in proportion to the temporal accuracy of the phase assignment.

8.6 The Heritability Gap

The current AD GWAS architecture, combined with rare-variant burden testing, captures approximately 30–35% of population heritability (Bellenguez et al., 2022). The remaining 60+% — sometimes called the "missing heritability" — has been variously attributed to rare variants below current detection thresholds, structural variants poorly tagged by SNP arrays, epigenetic and environmental contributions, and gene-gene interactions. The phase-weighted reading suggests an additional explanation: the linear additive model fits the phase-spanning master variables (APOE, TREM2) and the simple phase-restricted variants reasonably well, but it systematically underfits the combinatorial structure across phases, with the result that the variance explained by the model is a lower bound rather than an estimate of the true genetic contribution. The recovery of the missing heritability through phase-aware modeling is a testable prediction of the framework.

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9. Chapter VII — Relative Importance, Effect Sizes, and the Phase-Weighted Polygenic Score

9.1 The Three Metrics of Genetic Importance

The "importance" of a neurodegeneration gene is not a single quantity. Three distinct metrics, each well-defined and each measuring a different aspect of importance, can be applied to any gene of interest. The first is the **per-allele odds ratio at population frequency**, the canonical GWAS metric; the second is the **variance explained in polygenic risk**, the canonical population-genetics metric; the third is the **effector-pathway centrality** in functional network analyses, the canonical systems-biology metric. The three metrics agree only weakly with one another, and the disagreement is itself informative.

Ranked by per-allele odds ratio, the top genes are APOE (OR ~3.0 heterozygous, ~12 homozygous), TREM2 R47H (OR ~3.0), ABCA7 rare loss-of-function (OR ~2.0), SORL1 rare loss-of-function (OR ~2.5–3.0), and the various Mendelian genes (penetrance 90+%). This ranking emphasizes rare variants of large effect and identifies APOE as uniquely large among common variants.

Ranked by variance explained in PRS at population frequency, the top contributors are APOE (which alone accounts for ~6–8% of liability-scale variance at population frequency, more than any other gene by an order of magnitude), followed by BIN1, CR1, CLU, PICALM, MS4A6A, ABCA7, and TREM2 at variance contributions of 0.1–0.5% each. This ranking emphasizes common variants of small individual effect but high allele frequency.

Ranked by effector-pathway centrality in network analyses, the top genes are TREM2 (the single most central microglial signaling node), APOE (the single most central lipid-handling node), C1Q/C3 (the central complement node), MAPT (the central proteostasis node), and the convergent NAD□ and mitochondrial nodes (NMNAT2, SARM1, PINK1). This ranking emphasizes genes whose effector positions are sensitive to perturbation regardless of population allele frequency, and identifies a set of genes that may have outsized therapeutic importance even when their genetic-association signal is modest.

9.2 The Phase-Specific Effect Size

The conventional per-allele odds ratio is a population-averaged quantity. It averages across individuals at every age, every disease stage, and every phase of the underlying trajectory. The phase-specific effect size — the odds ratio that the same variant would carry if the test population were restricted to individuals in the phase in which the gene is load-bearing — is, in general, larger. The framework predicts that the phase-specific effect sizes of the microglial GWAS hits would substantially exceed their population-averaged effect sizes if measured in cohorts enriched for Phase II biology (i.e., individuals in the medial-temporal-lobe-amyloid, hippocampal-microglial-activation, oligodendrocyte-loss window). The same applies to the Phase I and Phase III genes.

The current literature has not systematically measured phase-specific effect sizes because the cohorts have not been phase-stratified. Cohort designs that incorporate phase-specific biomarker enrichment — PET-tau staging, CSF-tau and CSF-Aβ ratios, plasma p-tau217, plasma GFAP, plasma NfL, and emerging plasma biomarkers of PNN integrity — would enable the phase-specific effect-size measurements that the framework predicts.

9.3 The Architecture in One Hierarchy

Consolidating the three metrics into a single ordered hierarchy gives the following rank order:

Tier 1 (Master variables, phase-spanning): APOE.

Tier 2 (Mendelian anchors): APP, PSEN1, PSEN2; MAPT, GRN, C9ORF72; SNCA, LRRK2, GBA, PRKN, PINK1; SOD1, TARDBP, FUS; HTT.

Tier 3 (Rare-variant large-effect): TREM2 R47H, ABCA7 LOF, SORL1 LOF, PLCG2 P522R (protective), TBK1 LOF.

Tier 4 (Common-variant Phase-II microglial): CR1, CLU, BIN1, PICALM, MS4A6A/MS4A4A/MS4A4E, CD33, ABCA7 common, INPP5D, MEF2C, ABI3, SPI1, AXL, MERTK.

Tier 5 (Common-variant Phase III synaptic/PNN): ACAN, BCAN, TIMP3, ADAMTS4, PVALB-cluster, KCNC1, BIN1 (which is both Tier 4 and Tier 5), the Reelin-COLBOS modifier.

Tier 6 (Phase I bioenergetic, mostly without strong GWAS signal but mechanistically central): NMNAT2, SARM1, NAMPT, CD38, the sirtuin family, PINK1/PRKN/DJ-1 (Mendelian), OPA1, MFN2, POLG, TFAM, TFEB, ATG7, BECN1, OPTN, ATF4, the eIF2α-kinase family, TH, DBH, VMAT2.

The tier structure does not imply that lower tiers are less biologically important — Tier 6 contains the load-bearing Phase I machinery, which the framework argues is the earliest and most preventable phase — but rather that the genetic signal has been most easily detected in the upper tiers because the phenotype they affect (clinical AD diagnosis) is the terminal output of all three phases combined.

10. Chapter VIII — Therapeutic Implications: Genotype-Guided Phase-Matched Intervention

10.1 Phase I — PARP Inhibitors, NAD□ Precursors, SARM1 Inhibitors, ISR Modulators

The Phase I therapeutic landscape is anchored by interventions that preserve cellular NAD□ and mitochondrial function. PARP-1 inhibitors (veliparib, olaparib, talazoparib, niraparib, rucaparib) — already in clinical use in oncology — reduce NAD□ consumption by PARP-1 in the setting of chronic DNA damage, and their repurposing for Phase I neurodegeneration is in active development (Pieper laboratory; OSP entrants). The NAD□ precursors — nicotinamide riboside (NR), nicotinamide mononucleotide (NMN), nicotinic acid — supply substrate to the salvage pathway and have demonstrated safety in clinical trials with modest signals of cognitive benefit (Imai laboratory; Sinclair laboratory). The SARM1 inhibitors — DSRM-3716, NAD□-mimetic small molecules — supply the most direct intervention against the axonal-NAD□-collapse program and are entering clinical trials for chemotherapy-induced peripheral neuropathy with planned expansion to ALS and Phase I neurodegeneration. The ISR modulators — ISRIB, eIF2α-kinase-selective inhibitors — supply the cognitive-rescue arm of the Phase I therapeutic surface.

The genotype-guided enrichment strategy for Phase I trials is to enrich for individuals with high Phase I PRS scores (heavy loading on the NAD□, mitochondrial, autophagy, ISR, and LC-identity loci) and to deliver intervention during the Phase I window (age 30–55, in advance of measurable microglial activation by PET-glia imaging or plasma GFAP).

10.2 Phase II — TREM2 Agonists, Ferroptosis Inhibitors, Complement Inhibitors, TGF-β Restoration

The Phase II therapeutic landscape is anchored by interventions that restore microglial homeostasis, prevent ferroptotic oligodendrocyte loss, and constrain complement-mediated synaptic pruning. TREM2 agonist antibodies (AL002 from Alector, ATV:TREM2 from Denali, others) are in active clinical trials; their efficacy depends critically on the existence of a sufficient microglial population still capable of responding, which the framework predicts will be a function of the individual's position within Phase II. Ferroptosis inhibitors (liproxstatin-1 and ferrostatin-1 in preclinical development; deferiprone in oncology trials with planned AD expansion; emerging selective GPX4 stabilizers) target the oligodendrocyte vulnerability that defines Phase II. Complement inhibitors (ANX005/ANX007 from Annexon; anti-C3 from Apellis) constrain the synaptic-pruning arm of Phase II. TGF-β restoration strategies — recombinant TGF-β, SMAD3 activators, and the microglial-replacement strategies pioneered by Schwartz and colleagues — supply a category-distinct approach that restores rather than blocks the lost homeostatic state.

The genotype-guided enrichment strategy for Phase II trials is to enrich for individuals with high Phase II PRS scores (heavy loading on TREM2, CD33, MS4A, complement, ferroptosis, and oligodendroglial loci) and to deliver intervention during the Phase II window (age 50–70, with biomarker evidence of microglial activation but before fully consolidated cortical pathology).

10.3 Phase III — MMP-9 Inhibitors, PNN-Protective Agents, Gamma Entrainment

The Phase III therapeutic landscape is anchored by interventions that preserve perineuronal nets and the PV+ -interneuron-driven gamma-frequency machinery. MMP-9 inhibitors — the tetracycline-class antibiotics (minocycline, doxycycline) with their broad MMP inhibition and decades of CNS safety data, and the selective MMP-9 inhibitor JNJ0966 — supply the most direct Phase III intervention. PNN-protective agents — recombinant TIMP-3, chondroitinase-resistant CSPG analogs, and the LINK-protein-mimetics in preclinical development — offer category-distinct mechanisms. The 40-Hz gamma-entrainment strategy pioneered by Tsai and colleagues (Iaccarino et al., 2016; Adaikkan et al., 2019) supplies a non-pharmacological intervention that restores PV+ -driven gamma rhythm and has shown preliminary clinical efficacy.

The genotype-guided enrichment strategy for Phase III trials is to enrich for individuals with high Phase III PRS scores (heavy loading on PNN, matrix, PV+, and endocytic loci) and to deliver intervention during the Phase III window (age 65+ with cortical PET-tau and biomarker evidence of synaptic loss).

10.4 The Genotype × Phase Treatment Matrix

The integrated framework supplies a treatment matrix indexed jointly by genotype and biological phase. A young APOE4/4 carrier with high Phase I PRS receives NAD□ precursors, ISR modulators, and prophylactic PARP inhibition; the same individual at age 60 with high Phase II PRS adds TREM2 agonism, ferroptosis inhibition, and complement constraint; at age 75 with high Phase III PRS adds MMP-9 inhibition and gamma entrainment. The matrix predicts that the cumulative therapeutic benefit of phase-matched intervention exceeds that of single-target intervention by the cumulative phase-specific effect sizes, and that the trials needed to establish each component can be designed at substantially smaller sample sizes by appropriate genotype-and-phase enrichment.

11. Conclusion

The genetic architecture of neurodegeneration, read through the three temporal phases of Alzheimer's disease, is a layered architecture. The Mendelian genes anchor the system at high penetrance and identify five convergent effector themes — proteostasis, mitochondrial quality control, endolysosomal trafficking, RNA-binding-protein and stress-granule biology, and cytoskeletal-axonal integrity — that span the syndromic boundaries between AD, FTD, PD, ALS, and HD. APOE bridges the layers at population frequency, acting through distinct mechanisms in each of the three phases — lipid handling in Phase I, microglial state and LDAM in Phase II, and complement-mediated PNN attack in Phase III — and supplying the master-variable architecture that makes APOE genotype the single most informative piece of inherited risk information available to a clinician. The common-variant architecture distributes the remaining risk across the three phases, with the Phase II genes (TREM2, CD33, MS4A, complement, ferroptosis, oligodendroglial) most extensively populated, the Phase I genes (NAD□ network, mitochondrial quality control, ISR, LC identity) most mechanistically central, and the Phase III genes (PNN, matrix, PV+, endocytic) most directly tied to the cognitive trajectory.

The phase-weighted polygenic risk score that the dissertation has proposed reorganizes the use of genetic information for both prediction and intervention. As a predictor, it says not how much total risk a person carries but in which phase that risk is most likely to manifest — which is the question a clinician needs to answer when making decisions about preventive intervention. As an intervention guide, it pairs each individual's phase-weighted risk profile with the phase-matched therapeutic intervention that the framework predicts will be most effective at the relevant biological moment. The combined effect is to transform the conventional flat polygenic score — which has demonstrably underperformed clinical expectations — into a temporally-structured guide to phase-matched preventive medicine.

The framework also dissolves a long-standing tension between the Mendelian and common-variant literatures. The five convergent themes of Mendelian inheritance — proteostasis, mitochondrial quality control, endolysosomal trafficking, RNA-binding-protein biology, and cytoskeletal integrity — are precisely the themes that the common-variant architecture modifies at small individual effect sizes across the population. The Mendelian genes are the highly-penetrant tail of the same biological distribution that the common variants occupy at the mode; the framework

that the dissertation has proposed treats them as a single architecture viewed at two different allele-frequency scales, with the temporal-phase structure supplying the common organizing logic.

What remains is the empirical validation of the phase-weighted PRS at scale — the demonstration that phase-stratified cohorts yield phase-specific effect sizes substantially larger than the population-averaged effects, that phase-matched intervention produces clinical benefit that single-target intervention has failed to produce, and that the framework can be operationalized into clinical decision support that meaningfully changes patient outcomes. The framework is testable. The infrastructure to test it — the large-cohort biobanks, the plasma biomarker pipelines, the PET-tau and PET-glia imaging modalities, the polygenic-risk-score-computation infrastructure — is in place or close to it. The framework predicts that the next decade of AD trials, conducted under phase-matched enrichment, will produce effect sizes substantially larger than the previous decade's trials produced under undifferentiated enrichment, and that the temporal pharmacology that emerges from those trials will reorganize neurodegenerative-disease medicine from a one-drug-fits-all paradigm to a phase-matched precision medicine.

The genes that influence neurodegeneration are not a list. They are an architecture. The architecture is layered, and the layers are temporal. The genetic information that a person carries is most informatively read not as a single number but as a temporally-distributed profile that says when, in the life course, that information becomes load-bearing. This is the reading the dissertation has advanced, and it is the reading that the data — Mendelian, GWAS, single-cell, biomarker — increasingly supports.

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